



(19)

Europäisches Patentamt

European Patent Office

Officiel européen des brevets



(11)

EP 1 104 759 A1

(12)

EUROPEAN PATENT APPLICATION

(43) Date of publication:
06.06.2001 Bulletin 2001/23(51) Int Cl.7: C07D 405/14, C07D 417/14,
C07D 413/14, C07D 409/14,
C07D 401/14, A61K 31/506,
A61P 29/00

(21) Application number: 00310356.1

(22) Date of filing: 22.11.2000

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE TR
Designated Extension States:
AL LT LV MK RO SI

- Minich, Martha Lou, Pfizer Global Res. and Dev.
Groton, Connecticut 06340 (US)
- Lundy, Kristin Marie, Global Res. and Dev.
Groton, Connecticut 06340 (US)
- Cheng, Hengmiao, Pfizer Global Res. and Dev.
Groton, Connecticut 06340 (US)
- Li, Jin, Pfizer Global Research & Development
Groton, Connecticut 06340 (US)
- Bronk, Brian Scott, Pfizer Global Res. and Dev.
Groton, Connecticut 06340 (US)
- Sakya, Subas Man, Pfizer Global Res. and Dev.
Groton, Connecticut 06340 (US)

(30) Priority: 03.12.1999 US 168890 P

(71) Applicant: Pfizer Products Inc.
Groton, Connecticut 06340 (US)

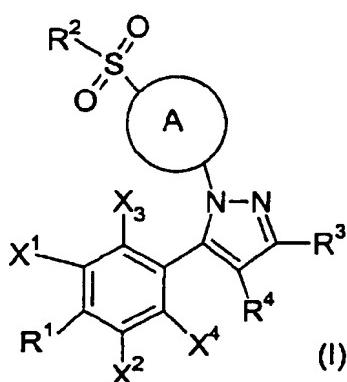
(72) Inventors:

- Ando, Kazuo,
Pfizer Global Research & Development
Chita-gun, Aichi-ken 470-2393 (JP)
- Kawamura, K.,
Pfizer Global Research & Development
Chita-gun, Aichi-ken 470-2393 (JP)
- Kato, Tomoki,
Pfizer Global Research & Development
Chita-gun, Aichi-ken 470-2393 (JP)

(74) Representative: Motion, Keith Robert et al
Pfizer Limited
Patents Department
Ramsgate Road
Sandwich, Kent CT13 9NJ (GB)

(54) Heteroaryl phenyl pyrazole compounds as anti-inflammatory/analgesic agents

(57) This invention relates to a compound of the formula:



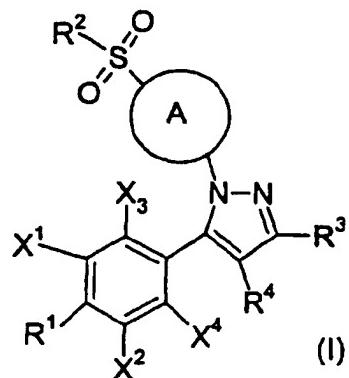
or a pharmaceutically acceptable salt thereof, wherein A and R¹ are each an optionally substituted 5 to 6-membered heteroaryl, wherein the heteroaryl is optionally fused to a carbocyclic ring or 5 to 6-heteroaryl; R² is (C₁-C₄)alkyl optionally substituted with halo, amino or an alkyl amino; R³ and R⁴ are each hydrogen, halo, (C₁-C₄)alkyl optionally substituted with halo and the like; and X¹ to X⁴ are each hydrogen, halo, hydroxy, (C₁-C₄)alkyl optionally substituted with halo and the like. These compounds have COX-2 inhibiting activity and thus useful for treating or preventing inflammation or other COX-2 related diseases.

Description**Technical Field**

- 5 [0001] This invention relates to heteroaryl-phenyl pyrazole derivatives and methods of treatment and pharmaceutical compositions for the treatment of cyclooxygenase mediated diseases. The compounds of this invention inhibit the biosynthesis of prostaglandins by intervention of the action of the enzyme cyclooxygenase on arachidonic acid, and are therefore useful in the treatment or alleviation of inflammation and other inflammation associated disorders, such as arthritis, neurodegeneration and colon cancer, in mammals, preferably humans, dogs, cats or livestock.
- 10 [0002] Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in treating pain and the signs and symptoms of arthritis because of their analgesic and anti-inflammatory activity. It is accepted that common NSAIDs work by blocking the activity of cyclooxygenase (COX), also known as prostaglandin G/H synthase (PGHS), the enzyme that converts arachidonic acid into prostanoids. Prostaglandins, especially prostaglandin E₂ (PGE₂), which is the predominant eicosanoid detected in inflammation conditions, are mediators of pain, fever and other symptoms associated with inflammation. Inhibition of the biosynthesis of prostaglandins has been a therapeutic target of anti-inflammatory drug discovery. The therapeutic use of conventional NSAIDs is, however, limited due to drug associated side effects, including life threatening ulceration and renal toxicity. An alternative to NSAIDs is the use of corticosteroids, however, long term therapy can also result in severe side effects.
- 15 [0003] The use of NSAIDs in the treatment or alleviation of inflammation and other inflammation associated disorders in dogs and cats has been more limited than that in humans: e.g., only three such NSAIDs have been approved by the Food and Drug Administration, Committee on Veterinary Medicine (FDA/CVM), for use in dogs in the United States, i.e., ETOGESIC® (etodolac), ARQUEL® (meclofenamic acid) and RIMADYL® (carprofen). Consequently, there is less experience and knowledge in veterinary medicine about safety and efficacy issues surrounding the use of NSAIDs in dogs. In veterinary medicine, for example, the most common indication for NSAIDs is the treatment of degenerative joint disease (DJD), which in dogs often results from a variety of developmental diseases, e.g., hip dysplasia and osteochondrosis, as well as from traumatic injuries to joints. In addition to the treatment of chronic pain and inflammation, NSAIDs are also useful in dogs for treating post-surgical acute pain, as well as for treating clinical signs associated with osteoarthritis.
- 20 [0004] Two forms of COX are now known, a constitutive isoform (COX-1) and an inducible isoform (COX-2) of which expression is upregulated at sites of inflammation (Vane, J. R.; Mitchell, J. A.; Appleton, I.; Tomlinson, A.; Bishop-Bailey, D.; Croxtoll, J.; Willoughby, D. A. *Proc. Natl. Acad. Sci. USA*, 1994, 91, 2046). COX-1 is thought to play a physiological role and to be responsible for gastrointestinal and renal protection. On the other hand, COX-2 appears to play a pathological role and is believed to be the predominant isoform present in inflammation conditions. A pathological role for prostaglandins has been implicated in a number of human disease states including rheumatoid arthritis and osteoarthritis, pyrexia, asthma, bone resorption, cardiovascular diseases, dysmenorrhea, premature labour, nephritis, nephrosis, atherosclerosis, hypotension, shock, pain, cancer, and Alzheimer disease. It is believed that compounds that would selectively inhibit the biosynthesis of prostaglandins by intervention of activity of the enzyme COX-2 on arachidonic acid would provide alternate therapy to the use of conventional NSAIDs or corticosteroids in that such compounds would exert anti-inflammatory effects without the adverse side effects associated with COX-1 inhibition.
- 25 [0005] A variety of sulfonylbenzene compounds which inhibit COX have been disclosed in patent publications (WO 97/16435, WO 97/14691, WO 96/19469, WO 96/36623, WO 96/03392, WO 96/03387, WO 97/727181, WO 96/936617, WO 96/19469, WO 96/08482, WO 95/00501, WO 95/15315, WO 95/15316, WO 95/15317, WO 95/15318, WO 97/13755, EP 0799523, EP 418845, and EP 554829). Especially, International Publication Number WO 97/11704 discloses pyrazole compounds substituted with optionally substituted aryl.
- 30

Brief Disclosure of the Invention

- [0006] The present invention provides a compound of the following formula:



or a pharmaceutically acceptable salt thereof, wherein

A is selected from the group consisting of

R¹ is selected from the group consisting of

a) (5- to 6-membered)-heteroaryl containing 1 to 4 ring heteroatoms independently selected from -N=, -NR-, -O-, or -S-, wherein said heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R'), formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R'), formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-;
 b) (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR-, -S- or -O-; wherein said heteroaryl is fused to a saturated, partially saturated or aromatic (5- to 7-membered)-carbocyclic ring; wherein either of said (5- to 6-membered)-heteroaryl ring or said fused saturated, partially saturated or aromatic (5- to 7-membered)-carbocyclic ring is optionally substituted with 1 to 2 substituents per ring, wherein said substituents are independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R'), formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R'), formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O); and
 c) (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR-, -S-, or -O-; wherein said heteroaryl is fused to a (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR-, -S- or -O-; wherein either of said (5- to 6-membered)-heteroaryl or said fused (5- to 6-membered)-heteroaryl is optionally substituted with one to two substituents per ring, wherein said substituents are independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R'), formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R'), formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-;

R² is selected from the group consisting of (C₁-C₄)alkyl optionally substituted with 1 to 3 halo;
 R³ and R⁴ are independently selected from the group consisting of hydrogen, halo, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-(C=O)-, cyano, nitro, carboxy, (C₁-C₄)alkoxy-(C=O)-, amino-(C=O)-, (C₁-C₄)alkyl-amino-(C=O)-, di[(C₁-C₄)alkyl]-amino-(C=O)-, N-[(C₁-C₄)alkyl]-N-phenyl-amino-(C=O)-, N-[(C₁-C₄)alkyl]-N-[(5- to 6-membered)-heteroaryl]amino-(C=O)-, wherein said (5- to 6)-membered heteroaryl contains 1 to 4 heteroatoms independently selected from -N=, -NR-, -O- and -S-; wherein each of said (C₁-C₄)alkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, phenyl, (C₁-C₄)alkoxy and (5- to 6-membered)-heteroaryl containing 1 to 4 heteroatoms independently selected from -N=, -NR-, -O- and -S-; wherein each of said R' is independently hydrogen or (C₁-C₄)alkyl; and
 X¹, X², X³ and X⁴ are independently selected from the group consisting of hydrogen, halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, (C₁-C₄)alkyl-amino-, di[(C₁-C₄)alkyl]-amino-, (C₁-C₄)alkyl-(C=O), (C₁-C₄)alkoxy-(C=O)- and amino-C(=O)-; wherein each said (C₁-C₄)alkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, amino, (C₁-C₄)alkyl-amino-, di[(C₁-C₄)alkyl]-amino-, hydroxy, carboxy, amino-(C=O)-, (C₁-C₄)alkyl-amino-C(=O)-, di[(C₁-C₄)alkyl]amino-C(=O)-, mercapto, (C₁-C₄)alkyl-S- and (C₁-C₄)alkoxy-(C=O)-.

[0007] The present invention also relates to the pharmaceutically acceptable acid addition salts of compounds of the formula I. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, glu-

conate, saccharate, benzoate, methanesulfonate, thanesulfonate, benzene sulfonate, p-toluen sulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)]salts.

[0008] The invention also relates to base addition salts of formula I. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of those compounds of formula I that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmacologically acceptable cations such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or watersoluble amine addition salts such as N-methylglucamine-(meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines.

[0009] The compounds of the invention may also exist in different tautomeric forms. This invention relates to all tautomers of formula I.

[0010] Certain compounds of the invention described herein contain one or more asymmetric centers and are capable of existing in various stereoisomeric forms. The present invention contemplates all such possible stereoisomers as well as their racemic and resolved, enantiomerically pure forms.

[0011] The term "treating", as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

[0012] The term "livestock animals" as used herein refers to domesticated quadrupeds, which includes those being raised for meat and various byproducts, e.g., a bovine animal including cattle and other members of the genus *Bos*, a porcine animal including domestic swine and other members of the genus *Sus*, an ovine animal including sheep and other members of the genus *Ovis*, domestic goats and other members of the genus *Capra*; domesticated quadrupeds being raised for specialized tasks such as use as a beast of burden, e.g., an equine animal including domestic horses and other members of the family Equidae, genus *Equus*, or for searching and sentinel duty, e.g., a canine animal including domestic dogs and other members of the genus *Canis*; and domesticated quadrupeds being raised primarily for recreational purposes, e.g., members of *Equus* and *Canis*, as well as a feline animal including domestic cats and other members of the family Felidae, genus *Felis*.

[0013] "Companion animals" as used herein refers to cats and dogs. As used herein, the term "dog(s)" denotes any member of the species *Canis familiaris*, of which there are a large number of different breeds. While laboratory determinations of biological activity may have been carried out using a particular breed, it is contemplated that the inhibitory compounds of the present invention will be found to be useful for treating pain and inflammation in any of these numerous breeds. Dogs represent a particularly preferred class of patients in that they are well known as being very susceptible to chronic inflammatory processes such as osteoarthritis and degenerative joint disease, which in dogs often results from a variety of developmental diseases, e.g., hip dysplasia and osteochondrosis, as well as from traumatic injuries to joints. Conventional NSAIDs, if used in canine therapy, have the potential for serious adverse gastrointestinal reactions and other adverse reactions including kidney and liver toxicity. Gastrointestinal effects such as single or multiple ulcerations, including perforation and hemorrhage of the esophagus, stomach, duodenum or small and large intestine, are usually debilitating, but can often be severe or even fatal.

[0014] The subject invention also includes isotopically-labelled compounds, which are identical to those recited in Formula I, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{170}Lu , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^3H , and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds of Formula I of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples and Preparations below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

[0015] This invention also encompasses pharmaceutical compositions containing prodrugs of compounds of the formula I. This invention also encompasses methods of treating or preventing disorders that can be treated or prevented by the inhibition of matrix metalloproteinases or the inhibition of mammalian repprolysin comprising administering prodrugs of compounds of the formula I. Compounds of formula I having free amino, amido, hydroxy, hydroxamic acid, sulfonamid or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues which are covalently joined

through peptide bonds to free amino, hydroxy or carboxylic acid groups of compounds of formula I. The amino acid residues include the 20 naturally occurring amino acids commonly designated by three letter symbols and also include 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline, homocysteine, homoserine, ornithine and methionine sulfone. Prodrugs also include compounds wherein carbonates, carbamates, amides and alkyl esters are covalently bonded to the above substituents of formula I through the carbonyl carbon prodrug sidechain.

[0016] One of ordinary skill in the art will appreciate that the compounds of the invention are useful in treating a diverse array of diseases. One of ordinary skill in the art will also appreciate that when using the compounds of the invention in the treatment of a specific disease that the compounds of the invention may be combined with various existing therapeutic agents used for that disease.

[0017] For the treatment of rheumatoid arthritis, the compounds of the invention may be combined with agents such as TNF- α inhibitors such as anti-TNF monoclonal antibodies and TNF receptor immunoglobulin molecules (such as Enbrel \circledR), low dose methotrexate, lefunimide, hydroxychloroquine, d-penicillamine, auranofin or parenteral or oral gold.

[0018] The compounds of the invention can also be used in combination with existing therapeutic agents for the treatment of osteoarthritis. Suitable agents to be used in combination include standard non-steroidal anti-inflammatory agents (hereinafter NSAID's) such as piroxicam, diclofenac, propionic acids such as naproxen, flurbiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin, COX-2 inhibitors such as celecoxib and rofecoxib, analgesics and intraarticular therapies such as corticosteroids and hyaluronic acids such as hyalgan and synvisc.

[0019] The active ingredient of the present invention may be administered in combination with inhibitors of other mediators of inflammation, comprising one or more members selected from the group consisting essentially of the classes of such inhibitors and examples thereof which include, matrix metalloproteinase inhibitors, aggrecanase inhibitors, TACE inhibitors, IL-1 processing and release inhibitors, ILRa, H₁-receptor antagonists; kinin-B₁- and B₂-receptor antagonists; prostaglandin inhibitors such as PGD₂, PGF₂, PGI₂ and PGE-receptor antagonists; thromboxane A2 (TXA2-) inhibitors; 5- and 12-lipoxygenase inhibitors; leukotriene LTC₄⁻, LTD₄/LTE₄⁻, and LTB₄⁻inhibitors; PAF-receptor antagonists; gold in the form of an aurothio group together with various hydrophilic groups; immunosuppressive agents, e.g., cyclosporine, azathioprine, and methotrexate; anti-inflammatory glucocorticoids; penicillamine; hydroxychloroquine; anti-gout agents, e.g., colchicine, xanthine oxidase inhibitors, e.g., allopurinol, and uricosuric agents, e.g., probenecid, sulfapyrazone, and benzbromarone.

[0020] The compounds of the present invention may also be used in combination with anticancer agents such as endostatin and angiostatin or cytotoxic drugs such as adriamycin, daunomycin, cis-platinum, etoposide, taxol, taxotere and alkaloids, such as vincristine, and antimetabolites such as methotrexate.

[0021] The compounds of the present invention may also be used in combination with anti-hypertensives and other cardiovascular drugs intended to offset the consequences of atherosclerosis, including hypertension, myocardial ischemia including angina, congestive heart failure, and myocardial infarction, selected from diuretics, vasodilators such as hydralazine, β -adrenergic receptor antagonists such as propranolol, angiotensin-11 converting enzyme inhibitors (ACE-inhibitors) such as enalapril used to treat geriatric mammals with mitral insufficiency, and enalapril alone and in combination with neutral endopeptidase inhibitors, angiotensin II receptor antagonists such as losartan, renin inhibitors, calcium channel blockers such as nifedipine, α 2-adrenergic agonists such as clonidine, α -adrenergic receptor antagonists such as prazosin, and HMG-CoA-reductase inhibitors (antihypercholesterolemics) such as lovastatin or atorvastatin.

[0022] The active ingredient of the present invention may also be administered in combination with one or more antibiotic, antifungal, antiprotozoal, antiviral or similar therapeutic agents.

[0023] The compounds of the present invention may also be used in combination with CNS agents such as antidepressants (such as sertraline), anti-Parkinsonian drugs (such as L-dopa, requip, mirapex, MAOB inhibitors such as selegiline and rasagiline, COMT inhibitors such as Tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, nicotine agonists, dopamine agonists and inhibitors of neuronal nitric oxide synthase), and anti-Alzheimer's drugs such as donepezil, tacrine, COX-2 inhibitors, propentofylline or metryfonate.

[0024] The compounds of the present invention may also be used in combination with osteoporosis agents such as roloxifene, droloxifene or fosamax and immunosuppressant agents such as FK-506 and rapamycin.

[0025] The present invention also relates to the formulation of the active agents of the present invention alone or with one or more other therapeutic agents which are to form the intended combination, including wherein said different drugs have varying half-lives, by creating controlled-release forms of said drugs with different release times which achieves relatively uniform dosing; or, in the case of non-human patients, a medicated feed dosage form in which said drugs used in the combination are present together in admixture in said feed composition. There is further provided in accordance with the present invention co-administration in which the combination of drugs is achieved by the simultaneous administration of said drugs to be given in combination; including co-administration by means of different dosage forms and routes of administration; the use of combinations in accordance with different but regular and con-

tinuous dosing schedules whereby desired plasma levels of said drugs involved are maintained in the mammals being treated, even though the individual mammals making up said combination are not being administered to said dog simultaneously.

5 [0026] This invention also relates to method for treating or preventing diseases or conditions mediated by cyclooxygenase-2 in a mammal including a human, dog, cat or livestock comprising administering an amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof effective for treating said diseases or conditions to said mammal.

10 [0027] This invention also relates to a pharmaceutical composition comprising an amount of a compound of formula I or a pharmaceutically acceptable salt thereof effective for treating or preventing diseases or conditions mediated by cyclooxygenase-2.

15 [0028] More specifically, this invention relates to a pharmaceutical composition for treating a disease or condition selected from the group consisting of diseases or conditions in which prostaglandins are implicated as pathogens, pain, fever, inflammation, rheumatic fever, symptoms associated with influenza and other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis including rheumatoid arthritis, degenerative joint disease or osteoarthritis, gout and ankylosing spondylitis, bursitis, burns, injuries following surgical and dental procedures, disease or conditions associated with cellular neoplastic transformations and metastatic tumor growth, cancer, colorectal cancer, breast and skin cancer, familiar adenomatous polyposis, cyclooxygenase-mediated proliferation disorders, cyclooxygenase-mediated proliferation disorders in diabetic retinopathy and tumor angiogenesis, prostanoid-induced smooth muscle contraction mediated by synthesis of contractile prostanoids, dysmenorrhea, premature labor, asthma, eosinophil related disorders, neurodegenerative diseases, Alzheimer's and Parkinson's disease, bone loss, osteoarthritis, peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis, recurrent of gastrointestinal lesions, gastrointestinal bleeding, coagulation, anemia, hypoprothrombinemia, haemophilia, bleeding problems; kidney disease and conditions prior to surgery of taking of anti-coagulants.

20 [0029] This Invention also relates to a method of treating or preventing inflammatory processes and diseases comprising administerin a compounds of formula I of this invention or its salt to a mammal including human, wherein said inflammatory processes and diseases are defind as above, and said inhibitory compound is used in combination with one or more other therapeutically active agents under the following conditions:

25 A. where a joint has become seriously inflamed as well as infected at the same time by bacteria, fungi, protozoa, and/or virus, said inhibitory compound is administered in combination with one or more antibiotic, antifungal, antiprotozoal, and/or antiviral therapeutic agents;

30 B. where a multi-fold treatment of pain and inflammation is desired, said inhibitory compound is administered in combination with inhibitors of other mediators of inflammation, comprising one or more members independently selected from the group consisting essentially of:

- (1) NSAIDs;
- (2) H₁-receptor antagonists;
- (3) kinin-B₁- and B₂-receptor antagonists;
- 40 (4) prostaglandin Inhibitors selected from the group consisting of PGD-, PGF-, PGI₂ -, and PGE-receptor antagonists;
- (5) thromboxane A2 (TXA₂) inhibitors;
- (6) 5-, 12- and 15-lipoxygenase inhibitors;
- (7) leukotriene LTC₄ -, LTD₄/LTE₄ -, and LTB₄ -inhibitors;
- 45 (8) PAF-receptor antagonists;
- (9) gold in the form of an aurothio group together with one or more hydrophilic groups;
- (10) immunosuppressive agents selected from the group consisting of cyclosporine, azathioprine, and methotrexate;
- (11) anti-inflammatory glucocorticoids;
- 50 (12) penicillamine;
- (13) hydroxychloroquine;
- (14) anti-gout agents including colchicine; xanthine oxidase inhibitors including allopurinol; and uricosuric agents selected from probenecid, sulfapyrazone, and benzboromarone;

55 C. where older mammals are being treated for disease conditions, syndroms and symptoms found in geriatric mammals, said inhibitory compound is administered in combination with one or more members independently select d from the group consisting ess ntially of:

(1) cognitive therapeutic agents to counteract memory loss and impairment;
 (2) anti-hypertensives and other cardiovascular drugs intended to offset the consequences of atherosclerosis, hypertension, myocardial ischemia, angina, congestive heart failure, and myocardial infarction, selected from the group consisting of:

- a. diuretics;
- b. vasodilators;
- c. β -adrenergic receptor antagonists;
- d. angiotensin-11 converting enzyme inhibitors (ACE-inhibitors), alone or optionally together with neutral endopeptidase inhibitors;
- e. angiotensin II receptor antagonists;
- f. renin inhibitors;
- g. calcium channel blockers;
- h. sympatholytic agents;
- i. α_2 -adrenergic agonists;
- j. α -adrenergic receptor antagonists; and
- k. HMG-CoA-reductase inhibitors (anti-hypercholesterolemics);

(3) antineoplastic agents selected from:

- a. antimitotic drugs selected from:
- i. vinca alkaloids selected from:
 - [1] vinblastine, and
 - [2] vincristine;

- (4) growth hormone secretagogues;
- (5) strong analgesics;
- (6) local and systemic anesthetics; and
- (7) H_2 -receptor antagonists, proton pump inhibitors, and other gastroprotective agents.

Detailed Disclosure of the Invention

[0030] The term "alkyl", as used herein, means a straight or branched saturated monovalent hydrocarbon radical including, but not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, secbutyl, *tert*-butyl and the like.

[0031] The term "alkoxy", as used herein, means an alkyl-O group wherein "alkyl" is defined as above.

[0032] The term "halo", as used herein, means fluoro, chloro, bromo or iodo, preferably F or Cl.

[0033] The term "(5 to 6-membered)-heteroaryl", as used herein, unless otherwise indicated, means a monocyclic aromatic hydrocarbon group having five to six ring atoms comprising one to four heteroatoms each independently selected from —N=, -NH-, -[N-(C₁-C₄)alkyl]-, -O- and -S-. Examples of the monocyclic ring systems are furyl, thieryl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, Isoxazolyl, oxazolyl, thiazolyl, Isothiazolyl, oxadiazolyl, oxatriazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, and the like.

[0034] The term "(5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR', -S- or -O-; wherein said heteroaryl is fused to a saturated, partially saturated or aromatic "(5- to 7-membered)carbocyclic ring," as used herein, unless otherwise indicated, means a bicyclic aromatic heterocyclic group having a first ring covalently bound to the pyrazole nucleus and containing five to six ring atoms comprising 1 to 2 heteroatoms each independently selected from -N=, -NH-, -[N-(C₁-C₄)alkyl]-, -O- and -S-; wherein said first ring is fused to a second ring comprising a (5 to 7 membered)-carbocycle, wherein the 5- to 7- members include the carbon atoms common to both rings. Examples of said bicyclic ring systems are benzofuranyl, isobenzofuranyl, benzothiophenyl, isobenzothiophenyl, indolyl, isoindolyl, cyclopentapyridyl, pyranopyrrolyl, indazolyl, indoxazinyl, benzoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, pyridopyridyl and the like.

[0035] The term "(5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR', -S-, or -O-; wherein said heteroaryl is fused to a (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR', -S- or -O-;" as used herein, unless otherwise indicated, means a bicyclic aromatic heterocyclic group having a first ring covalently bound to the pyrazole nucleus and containing five to six ring atoms comprising one to two heteroatoms each independently selected from -N=, -NH-, -[N-(C₁-C₄)alkyl]-, -O- and -S-; wherein said first ring is fused to a second ring comprising a 5 to 7 membered heteroaryl, wherein said second 5 to 7 members include the atoms common to both rings. Examples of said bicyclic ring systems are pyridopyridyl or the like.

[0036] The term "treating", as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment" as used herein refers to the act of treating, as "treating" is defined immediately above.

[0037] An embodiment of the present invention includes compounds of formula I, referred to as the A(a) Group compounds, wherein A is (5- to 6-membered)- heteroaryl containing 1 to 4 ring heteroatoms independently selected from -N=, -NR', -O-, or -S-, wherein said heteroaryl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R'), formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl may optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R'), formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein preferred A is selected from the group consisting of (5- to 6-membered)- heteroaryl containing 1 to 4 ring heteroatoms independently selected from -N=, -NR', -O-, or -S-, wherein said heteroaryl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R'), formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl may optionally be substituted with 1 to 3 halo.

[0038] A subgenus of the embodiment of the A(a) group of compounds are those compounds (designated the subgenus A(a)-R¹(a)) wherein A is defined above as A(a) and R¹, referred to hereinafter as R¹(a), is (5- to 6-membered)- heteroaryl containing 1 to 4 ring heteroatoms independently selected from -N=, -NR', -O-, or -S-, wherein said heteroaryl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R'), formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R'), formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein preferred R¹ is selected from the group consisting of (5- to 6-membered)- heteroaryl containing 1 to 4 ring heteroatoms independently selected from -N=, -NR', -O-, or -S-, wherein said heteroaryl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-(C=O)-, hydroxy, cyano and amino; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl may optionally be substituted with 1 to 3 halo.

[0039] Another subgenus of the embodiment of the A(a) group of compounds are those compounds (designated the subgenus A(a)-R¹(b)) wherein A is defined above as A(a) and R¹, referred to hereinafter as R¹(b), is (5- to 6-membered)- heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR', -S- or -O-; wherein said heteroaryl is fused to a saturated, partially saturated or aromatic (5- to 7membered)-carbocyclic ring; wherein either of said (5- to 6-membered)-heteroaryl ring or said fused saturated, partially saturated or aromatic (5- to 7-membered)-carbocyclic ring is optionally substituted with 1 to 2 substituents per ring, wherein said substituents are independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R'), formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R'), formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein preferred R¹ is selected from the group consisting of (5- to 6-membered)-heteroaryl containing 1 ring heteroatom selected from the group consisting of -N=, -NR', -S- or -O-; wherein said heteroaryl is fused to an aromatic (6-membered)-carbocyclic ring; wherein either of said (5- to 6-membered)-heteroaryl ring or said fused aromatic (6-membered)-carbocyclic ring may optionally be substituted with 1 to 2 substituents per ring, wherein said substituents are independently selected from the group consisting of halo and (C₁-C₄)alkyl; wherein R' is hydrogen or (C₁-C₄)alkyl.

[0040] Another subgenus of the embodiment of the A(a) group of compounds are those compounds (designated the subgenus A(a)-R¹(c)) wherein A is as defined above as A(a) and R¹, referred to hereinafter as R¹(c), is (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR', -S-, or -O-; wherein said heteroaryl is fused to a (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR', -S- or -O-; wherein either of said (5- to 6-membered)-

heteroaryl or said fused (5- to 6-membered)heteroaryl is optionally substituted with one to two substituents per ring; wherein said substituents are independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N-

(R'), formyl, (C₁-C₄)alkyl-(C=O) and (C₁-C₄)alkoxy-(C=O); wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₁-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R'), formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O).

[0041] Another embodiment of the invention of the A(a) group of compounds, including the subgenera A(a)-R¹(a), A(a)-R¹(b) and A(a)-R¹(c), are those compounds wherein A is as defined above as A(a), R¹ is as defined above as R¹(a, b or c) and one of R³ or R⁴ is hydrogen (wherein R^{3,4a} refers to R³ as hydrogen and wherein R^{3,4b} refers to R⁴ as hydrogen). Such subgenera can be designated A(a)-R^{3,4a} and A(a)-R^{3,4b}, and sub-subgenera A(a)-R¹(a)-R^{3,4a}, A(a)-R¹(a)-R^{3,4b}, A(a)-R¹(b)-R^{3,4a}, A(a)-R¹(b)-R^{3,4b}, A(a)-R¹(c)-R^{3,4a} and A(a)-R¹(c)-R^{3,4b}.

[0042] Another embodiment of the invention of compounds of the formula A(a) compounds, including the subgenera A(a)-R¹(a), A(a)-R¹(b), A(a)-R¹(c), A(a)-R^{3,4a} and A(a)-R^{3,4b} and sub-subgenera A(a)-R¹(a)-R^{3,4a}, A(a)-R¹(a)-R^{3,4b}, A(a)-R¹(b)-R^{3,4a}, A(a)-R¹(b)-R^{3,4b}, A(a)-R¹(c)-R^{3,4a} and A(a)-R¹(c)-R^{3,4b}, are those compounds wherein two, three or four of X¹, X², X³ and X⁴ are hydrogen (wherein X^{1-4a} refers to two of X¹ - X⁴ as hydrogen, X^{1-4b} refers to three of X¹ - X⁴ as hydrogen and X^{1-4c} refers to four of X¹ - X⁴ as hydrogen). Such subgenera can be designated A(a)-X^{1-4a}, A(a)-X^{1-4b}, A(a)-X^{1-4c} and A(a)-X^{1-4d}. Such sub-subgenera can be designated A(a)-R¹(a)-X^{1-4a}, A(a)-R¹(b)-X^{1-4a}, A(a)-R¹(c)-X^{1-4a}, A(a)-R^{3,4b}-X^{1-4b}, A(a)-R¹(a)-X^{1-4c} A(a)-R¹(b)-X^{1-4c}, A(a)-R¹(c)-X^{1-4c}, A(a)-R^{3,4b}-X^{1-4c} and A(a)-R¹(a)-R^{3,4b}-X^{1-4c}. Sub-sub-subgenera can be designated A(a)-R¹(a)-R^{3,4a}-X^{1-4a}, A(a)-R¹(a)-R^{3,4b}-X^{1-4a}, A(a)-R¹(b)-R^{3,4a}-X^{1-4a}, A(a)-R¹(b)-R^{3,4b}-X^{1-4a}, A(a)-R¹(c)-R^{3,4a}-X^{1-4a}, A(a)-R¹(c)-R^{3,4b}-X^{1-4a} and A(a)-R¹(c)-R^{3,4c}-X^{1-4a}.

[0043] A group of compounds which is preferred among the A(a) Group compounds, including subgenera A(a)-R¹(a), A(a)-R¹(b), A(a)-R¹(c), are those compounds (designated subgenera A(a)-R^{3a}, and sub-subgenera A(a)-R¹(a)-R^{3a}, A(a)-R¹(b)-R^{3a}, A(a)-R¹(c)-R^{3a} including any preferences) wherein A is as defined above as A(a), R¹ is as defined above as R¹(a, b or c) and R³ is selected from hydrogen; halo; (C₁-C₄)alkyl optionally substituted with 1 to 3 halo; (C₁-C₄)alkoxy; (C₁-C₄)alkyl-O-C(=O)- and cyano (wherein said preferred R³ is referred to as R^{3a}).

[0044] Another group of compounds which is preferred among the A(a) Group of compounds, including subgenera A(a)-R¹(a), A(a)-R¹(b), A(a)-R¹(c), A(a)-R^{3a} sub-subgenera A(a)-R¹(a)-R^{3a}, A(a)-R¹(b)-R^{3a}, A(a)-R¹(c)-R^{3a}, are those compounds (designated subgenera A(a)-R^{4a}, and sub-subgenera A(a)-R¹(a)-R^{4a}, A(a)-R¹(b)-R^{4a}, A(a)-R¹(c)-R^{4a}, A(a)-R¹(a)-R^{3a}-R^{4a}, A(a)-R¹(b)-R^{3a}-R^{4a}, A(a)-R¹(c)-R^{3a}-R^{4a}), wherein A is as defined above as A(a), R¹ is as defined above as R¹(a, b or c), R³ is defined above as R^{3a} and R⁴ is selected from hydrogen; halo; (C₁-C₄)alkyl optionally substituted with 1 to 3 halo; (C₁-C₄)alkoxy; (C₁-C₄)alkyl-O-C(=O)and cyano (wherein said preferred R⁴ is R^{4a}).

[0045] Another group of compounds which is preferred among each A(a) Group of compounds, including subgenera A(a)-R¹(a), A(a)-R¹(b), A(a)-R¹(c), A(a)-R^{3a} A(a)-R^{4a}, sub-subgenera A(a)-R¹(a)-R^{3a}, A(a)-R¹(b)-R^{3a}, A(a)-R¹(c)-R^{3a}, A(a)-R¹(a)-R^{4a}, A(a)-R¹(b)-R^{4a}, A(a)-R¹(c)-R^{4a}, and A(a)-R^{3a}-R^{4a}, and sub-sub-subgenera A(a)-R¹(a)-R^{3a}-R^{4a}, A(a)-R¹(b)-R^{3a}-R^{4a}, A(a)-R¹(c)-R^{3a}-R^{4a} are those compounds (designated subgenera A(a)-X^{1-4d} and sub-subgenera A(a)-R¹(a)-X^{1-4d}, A(a)-R¹(b)-X^{1-4d}, A(a)-R¹(c)-X^{1-4d}, A(a)-R^{3a}-X^{1-4d} and A(a)-R^{4a}-X^{1-4d} and sub-sub-subgenera A(a)-R¹(a)-R^{3a}-X^{1-4d}, A(a)-R¹(b)-R^{3a}-X^{1-4d}, A(a)-R¹(c)-R^{3a}-X^{1-4d}, A(a)-R¹(a)-R^{4a}-X^{1-4d}, A(a)-R¹(b)-R^{4a}-X^{1-4d}, A(a)-R¹(c)-R^{4a}-X^{1-4d} and sub-sub-sub-subgenera A(a)-R¹(a)-R^{3a}-R^{4a}-X^{1-4d}, A(a)-R¹(b)-R^{3a}-R^{4a}-X^{1-4d} A(a)-R¹(c)-R^{3a}-R^{4a}-X^{1-4d}) wherein X¹ and X² are each independently selected from hydrogen; halo; (C₁-C₄)alkyl optionally substituted with 1 to 3 halo; cyano and (C₁-C₄)alkoxy (wherein X^{1-4d} refers to said preferred X¹ and X²).

[0046] A group of compounds which is preferred among each A(a) Group of compounds, including subgenera A(a)-R¹(a), A(a)-R¹(b), A(a)-R¹(c), A(a)-R^{3a} A(a)-R^{4a}, sub-subgenera A(a)-R¹(a)-R^{3a}, A(a)-R¹(b)-R^{3a}, A(a)-R¹(c)-R^{3a}, A(a)-R¹(a)-R^{4a}, A(a)-R¹(b)-R^{4a}, A(a)-R¹(c)-R^{4a}, A(a)-R^{3a}-R^{4a} and sub-sub-subgenera A(a)-R¹(a)-R^{3a}-R^{4a}, A(a)-R¹(b)-R^{3a}-R^{4a}, A(a)-R¹(c)-R^{3a}-R^{4a} are those compounds (designated subgenera A(a)-X^{1-4e} and sub-subgenera A(a)-R¹(a)-X^{1-4e}, A(a)-R¹(b)-X^{1-4e}, A(a)-R¹(c)-X^{1-4e}, A(a)-R^{3a}-X^{1-4e} and A(a)-R^{4a}-X^{1-4e} and sub-sub-subgenera A(a)-R¹(a)-R^{3a}-X^{1-4e}, A(a)-R¹(b)-R^{3a}-X^{1-4e}, A(a)-R¹(c)-R^{3a}-X^{1-4e}, A(a)-R¹(a)-R^{4a}-X^{1-4e}, A(a)-R¹(b)-R^{4a}-X^{1-4e}, A(a)-R¹(c)-R^{4a}-X^{1-4e}, A(a)-R^{3a}-R^{4a}-X^{1-4e} and sub-sub-sub-subgenera A(a)-R¹(a)-R^{3a}-R^{4a}-X^{1-4e} A(a)-R¹(b)-R^{3a}-R^{4a}-X^{1-4e}, A(a)-R¹(c)-R^{3a}-R^{4a}-X^{1-4e}) wherein X³ and X⁴ are each independently selected from hydrogen; halo; (C₁-C₄)alkyl optionally substituted with 1 to 3 halo; cyano and (C₁-C₄)alkoxy (wherein X^{1-4e} refers to said preferred X³ and X⁴).

[0047] An embodiment of the present invention includes compounds of formula I, referred to as the A(b) Group compounds, wherein A is (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR¹, -S- or -O-; wherein said heteroaryl is fused to a saturated, partially saturated

or aromatic (5- to 7-m mb red)-carbocyclic ring; wherein either of said (5- to 6-m mber d)-heteroaryl ring or said fused saturated, partially saturated or aromatic (5- to 7-m mb red)-carbocyclic ring may optionally be substituted with 1 to 2 substituents per ring, wherein said substituents are independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R'), formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R'), formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-.

[0048] A subgenus of the embodiment of the A(b) group of compounds are those compounds (designated the subgenus A(b)-R¹(a)) wherein A is defined above as A(b) and R¹, referred to hereinafter as R¹(a), is (5- to 6-membered)-heteroaryl containing 1 to 4 ring heteroatoms independently selected from -N=, -NR', -O-, or -S-, wherein said heteroaryl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R'), formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R'), formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein preferred R¹ is selected from the group consisting of (5- to 6-membered)-heteroaryl containing 1 to 4 ring heteroatoms independently selected from -N=, -NR', -O-, or -S-, wherein said heteroaryl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-(C=O)-, hydroxy, cyano and amino; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl may optionally be substituted with 1 to 3 halo.

[0049] Another subgenus of the embodiment of the A(b) group of compounds are those compounds (designated the subgenus A(b)-R¹(b)) wherein A is defined above as A(b) and R¹, referred to hereinafter as R¹(b), is (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR', -S- or -O-; wherein said heteroaryl is fused to a saturated, partially saturated or aromatic (5- to 7-membered)-carbocyclic ring; wherein either of said (5- to 6-membered)-heteroaryl ring or said fused saturated, partially saturated or aromatic (5- to 7-membered)-carbocyclic ring is optionally substituted with 1 to 2 substituents per ring, wherein said substituents are independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R'), formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R'), formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein preferred R¹ is selected from the group consisting of (5- to 6-membered)-heteroaryl containing 1 ring heteroatom selected from the group consisting of -N=, -NR', -S- or -O-; wherein said heteroaryl is fused to an aromatic (6-membered)-carbocyclic ring; wherein either of said (5- to 6-membered)-heteroaryl ring or said fused aromatic (6-membered)-carbocyclic ring may optionally be substituted with 1 to 2 substituents per ring, wherein said substituents are independently selected from the group consisting of halo and (C₁-C₄)alkyl; wherein R' is hydrogen or (C₁-C₄)alkyl.

[0050] Another subgenus of the embodiment of the A(b) group of compounds are those compounds (designated the subgenus A(b)-R¹(c)) wherein A is as defined above as A(b) and R¹, referred to hereinafter as R¹(c), is (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR', -S-, or -O-; wherein said heteroaryl is fused to a (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR', -S- or -O-; wherein either of said (5- to 6-membered)-heteroaryl or said fused (5- to 6-membered)-heteroaryl is optionally substituted with one to two substituents per ring, wherein said substituents are independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R'), formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R'), formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-.

alkyl-S-, amino, (C_1 - C_4)alkylamino, di[(C_1 - C_4)alkyl]amino, amido, (C_1 - C_4)alkylamido, di[(C_1 - C_4)alkyl]amido, (C_1 - C_4)alkyl-(C=O)-O-, (C_1 - C_4)alkyl-(C=O)-N(R')-, formyl, (C_1 - C_4)alkyl-(C=O)- and (C_1 - C_4)alkoxy-(C=O)-.

[0051] Another embodiment of the invention of the A(b) group of compounds, including the subgenera A(b)-R¹(a), A(b)-R¹(b) and A(b)-R¹(c), are those compounds wherein A is as defined above as A(b), R¹ is as defined above as R¹(a, b or c) and one of R³ or R⁴ is hydrogen (wherein R^{3,4a} refers to R³ as hydrogen and wherein R^{3,4b} refers to R⁴ as hydrogen). Such subgenera can be designated A(b)-R^{3,4a} and A(b)-R^{3,4b}, and sub-subgenera A(b)-R¹(a)-R^{3,4b}, A(b)-R¹(b)-R^{3,4a}, A(b)-R¹(b)-R^{3,4b}, A(b)-R¹(c)-R^{3,4a} and A(b)-R¹(c)-R^{3,4b}.

[0052] Another embodiment of the invention of compounds of the formula A(b) compounds, including the subgenera A(b)-R¹(a), A(b)-R¹(b), A(b)-R¹(c), A(b)-R^{3,4a} and A(b)-R^{3,4b} and sub-subgenera A(b)-R¹(a)-R^{3,4a}, A(b)-R¹(a)-R^{3,4b}, A(b)-R¹(b)-R^{3,4a}, A(b)-R¹(b)-R^{3,4b}, A(b)-R¹(c)-R^{3,4a} and A(b)-R¹(c)-R^{3,4b}, are those compounds wherein two, three or four of X¹, X², X³ and X⁴ are hydrogen (wherein X^{1-4a} refers to two of X¹-X⁴ as hydrogen, X^{1-4b} refers to three of X¹-X⁴ as hydrogen and X^{1-4c} refers to four of X¹-X⁴ as hydrogen). Such subgenera can be designated A(b)-X^{1-4a}, A(b)-X^{1-4b}, A(b)-X^{1-4c}. Such sub-subgenera can be designated A(b)-R¹(a)-X^{1-4a}, A(b)-R¹(b)-X^{1-4a}, A(b)-R¹(c)-X^{1-4a}, A(b)-R^{3,4a}-X^{1-4a} and A(b)-R^{3,4b}-X^{1-4a}, A(b)-R¹(a)-X^{1-4c}, A(b)-R¹(b)-X^{1-4c}, A(b)-R¹(c)-X^{1-4c}, A(b)-R^{3,4a}-X^{1-4c} and A(b)-R^{3,4b}-X^{1-4c}. Sub-sub-subgenera can be designated A(b)-R¹(a)-R^{3,4a}-X^{1-4a}, A(b)-R¹(a)-R^{3,4b}-X^{1-4a}, A(b)-R¹(b)-R^{3,4a}-X^{1-4a}, A(b)-R¹(b)-R^{3,4b}-X^{1-4a}, A(b)-R¹(c)-R^{3,4a}-X^{1-4a} and A(b)-R¹(c)-R^{3,4b}-X^{1-4a}, A(b)-R¹(a)-R^{3,4a}-X^{1-4b}, A(b)-R¹(a)-R^{3,4b}-X^{1-4b}, A(b)-R¹(b)-R^{3,4a}-X^{1-4b}, A(b)-R¹(b)-R^{3,4b}-X^{1-4b}, A(b)-R¹(c)-R^{3,4a}-X^{1-4b}, A(b)-R¹(c)-R^{3,4b}-X^{1-4b} and A(b)-R¹(c)-R^{3,4b}-X^{1-4c}, A(b)-R¹(a)-R^{3,4a}-X^{1-4c}, A(b)-R¹(b)-R^{3,4a}-X^{1-4c}, A(b)-R¹(c)-R^{3,4a}-X^{1-4c} and A(b)-R¹(c)-R^{3,4b}-X^{1-4c}.

[0053] A group of compounds which is preferred among the A(b) Group compounds, including subgenera A(b)-R¹(a), A(b)-R¹(b), A(b)-R¹(c), are those compounds (designated subgenera A(b)-R^{3a}, and sub-subgenera A(b)-R¹(a)-R^{3a}, A(b)-R¹(b)-R^{3a}, A(b)-R¹(c)-R^{3a} including any preferences) wherein A is as defined above as A(b), R¹ is as defined above as R¹(a, b or c) and R³ is selected from hydrogen; halo; (C_1 - C_4)alkyl optionally substituted with 1 to 3 halo; (C_1 - C_4)alkoxy; (C_1 - C_4)alkyl-O-C(=O)- and cyano (wherein said preferred R³ is referred to as R^{3a}).

[0054] Another group of compounds which is preferred among the A(b) Group of compounds, including subgenera A(b)-R¹(a), A(b)-R¹(b), A(b)-R¹(c), A(b)-R^{3a}, sub-subgenera A(b)-R¹(a)-R^{3a}, A(b)-R¹(b)-R^{3a}, A(b)-R¹(c)-R^{3a}, are those compounds (designated subgenera A(b)-R^{4a}, and sub-subgenera A(b)-R¹(a)-R^{4a}, A(b)-R¹(b)-R^{4a}, A(b)-R¹(c)-R^{4a}, A(b)-R¹(a)-R^{3a}-R^{4a}, A(b)-R¹(b)-R^{3a}-R^{4a}, A(b)-R¹(c)-R^{3a}-R^{4a}), wherein A is as defined above as A(b), R¹ is as defined above as R¹(a, b or c), R³ is defined above as R^{3a} and R⁴ is selected from hydrogen; halo; (C_1 - C_4)alkyl optionally substituted with 1 to 3 halo; (C_1 - C_4)alkoxy; (C_1 - C_4)alkyl-O-C(=O)- and cyano (wherein said preferred R⁴ is R^{4a}).

[0055] Another group of compounds which is preferred among each A(b) Group of compounds, including subgenera A(b)-R¹(a), A(b)-R¹(b), A(b)-R¹(c), A(b)-R^{3a}, A(b)-R^{4a}, sub-subgenera A(b)-R¹(a)-R^{3a}, A(b)-R¹(b)-R^{3a}, A(b)-R¹(c)-R^{3a}, A(b)-R¹(a)-R^{4a}, A(b)-R¹(b)-R^{4a}, A(b)-R¹(c)-R^{4a}, and A(b)-R^{3a}-R^{4a}, and sub-sub-subgenera A(b)-R¹(a)-R^{3a}-R^{4a}, A(b)-R¹(b)-R^{3a}-R^{4a}, A(b)-R¹(c)-R^{3a}-R^{4a}) are those compounds (designated subgenera A(b)-X^{1-4d} and sub-subgenera A(b)-R¹(a)-X^{1-4d}, A(b)-R¹(b)-X^{1-4d}, A(b)-R¹(c)-X^{1-4d} and A(b)-R^{3a}-X^{1-4d} and sub-sub-subgenera A(b)-R¹(a)-R^{3a}-X^{1-4d}, A(b)-R¹(b)-R^{3a}-X^{1-4d}, A(b)-R¹(c)-R^{3a}-X^{1-4d}, A(b)-R¹(a)-R^{4a}-X^{1-4d}, A(b)-R¹(b)-R^{4a}-X^{1-4d}, A(b)-R¹(c)-R^{4a}-X^{1-4d}, A(b)-R^{3a}-R^{4a}-X^{1-4d}, and sub-sub-sub-subgenera A(b)-R¹(a)-R^{3a}-R^{4a}-X^{1-4d}, A(b)-R¹(b)-R^{3a}-R^{4a}-X^{1-4d}, A(b)-R¹(c)-R^{3a}-R^{4a}-X^{1-4d}) wherein X¹ and X² are each independently selected from hydrogen; halo; (C_1 - C_4)alkyl optionally substituted with 1 to 3 halo; cyano and (C_1 - C_4)alkoxy (wherein X^{1-4d} refers to said preferred X¹ and X²).

[0056] A group of compounds which is preferred among each A(b) Group of compounds, including subgenera A(b)-R¹(a), A(b)-R¹(b), A(b)-R¹(c), A(b)-R^{3a}, A(b)-R^{4a}, sub-subgenera A(b)-R¹(a)-R^{3a}, A(b)-R¹(b)-R^{3a}, A(b)-R¹(c)-R^{3a}, A(b)-R¹(a)-R^{4a}, A(b)-R¹(b)-R^{4a}, A(b)-R¹(c)-R^{4a}, A(b)-R^{3a}-R^{4a}, A(b)-R¹(c)-R^{3a}-R^{4a}) are those compounds (designated subgenera A(b)-X^{1-4e} and sub-subgenera A(b)-R¹(a)-X^{1-4e}, A(b)-R¹(b)-X^{1-4e}, A(b)-R¹(c)-X^{1-4e} and A(b)-R^{3a}-X^{1-4e} and sub-sub-subgenera A(b)-R¹(a)-R^{3a}-X^{1-4e}, A(b)-R¹(b)-R^{3a}-X^{1-4e}, A(b)-R¹(c)-R^{3a}-X^{1-4e}, A(b)-R¹(b)-R^{4a}-X^{1-4e}, A(b)-R¹(c)-R^{4a}-X^{1-4e}, A(b)-R^{3a}-R^{4a}-X^{1-4e}, and sub-sub-sub-subgenera A(b)-R¹(a)-R^{3a}-R^{4a}-X^{1-4e}, A(b)-R¹(b)-R^{3a}-R^{4a}-X^{1-4e}, A(b)-R¹(c)-R^{3a}-R^{4a}-X^{1-4e}) wherein X³ and X⁴ are each independently selected from hydrogen; halo; (C_1 - C_4)alkyl optionally substituted with 1 to 3 halo; cyano and (C_1 - C_4)alkoxy (wherein X^{1-4e} refers to said preferred X³ and X⁴).

[0057] An embodiment of the present invention includes compounds of formula I, referred to as the A(c) Group compounds, wherein A is (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR¹, -S-, or -O-; wherein said heteroaryl is fused to a (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR¹, -S- or -O-; wherein either of said (5- to 6-membered)-heteroaryl or said fused (5- to 6-membered)-heteroaryl is optionally substituted with one to two substituents per ring, wherein said substituents are independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C_1 - C_4)alkyl, (C_2 - C_4)alkenyl, (C_2 - C_4)alkynyl, (C_1 - C_4)alkoxy, (C_1 - C_4)alkyl-S-, amino, (C_1 - C_4)alkylamino, di[(C_1 - C_4)alkyl]amino, amido, (C_1 - C_4)alkylamido, di[(C_1 - C_4)alkyl]amido, (C_1 - C_4)alkyl-(C=O)-O-, (C_1 - C_4)alkyl-(C=O)-N(R')-, formyl, (C_1 - C_4)alkyl-(C=O)- and (C_1 - C_4)alkoxy-(C=O)-; wherein R' is hydrogen or (C_1 - C_4)alkyl; wherein each of said (C_1 - C_4)alkyl may optionally be substituted with 1 to 3 substituents independ-

ently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-..

5 [0058] A subgenus of the embodiment of the A(c) group of compounds are those compounds (designated the subgenus A(c)-R¹(a)) wherein A is defined above as A(c) and R¹, referred to hereinafter as R¹(a), is (5- to 6-membered)-heteroaryl containing 1 to 4 ring heteroatoms independently selected from -N=, -NR', -O-, or -S-, wherein said heteroaryl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein preferred R¹ is selected from the group consisting of (5- to 6-membered)-heteroaryl containing 1 to 4 ring heteroatoms independently selected from -N=, -NR', -O-, or -S-, wherein said heteroaryl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-(C=O)-, hydroxy, cyano and amino; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl may optionally be substituted with 1 to 3 halo.

10 [0059] Another subgenus of the embodiment of the A(c) group of compounds are those compounds (designated the subgenus A(c)-R¹(b)) wherein A is defined above as A(c) and R¹, referred to hereinafter as R¹(b), is (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR', -S- or -O-; wherein said heteroaryl is fused to a saturated, partially saturated or aromatic (5- to 7-membered)-carbocyclic ring; wherein either of said (5- to 6-membered)-heteroaryl ring or said fused saturated, partially saturated or aromatic (5- to 7-membered)-carbocyclic ring is optionally substituted with 1 to 2 substituents per ring, wherein said substituents are independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein preferred R¹ is selected from the group consisting of (5- to 6-membered)-heteroaryl containing 1 ring heteroatom selected from the group consisting of -N=, -NR', -S- or -O-; wherein said heteroaryl is fused to an aromatic (6-membered)-carbocyclic ring; wherein either of said (5- to 6-membered)-heteroaryl ring or said fused aromatic (6-membered)-carbocyclic ring may optionally be substituted with 1 to 2 substituents per ring, wherein said substituents are independently selected from the group consisting of halo and (C₁-C₄)alkyl; wherein R' is hydrogen or (C₁-C₄)alkyl.

15 [0060] Another subgenus of the embodiment of the A(c) group of compounds are those compounds (designated the subgenus A(c)-R¹(c)) wherein A is as defined above as A(c) and R¹, referred to hereinafter as R¹(c), is (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR', -S-, or -O-; wherein said heteroaryl is fused to a (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR', -S- or -O-; wherein either of said (5- to 6-membered)-heteroaryl or said fused (5- to 6-membered)-heteroaryl is optionally substituted with one to two substituents per ring, wherein said substituents are independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-.

20 [0061] Another embodiment of the invention of the A(c) group of compounds, including the subgenera A(c)-R¹(a), A(c)-R¹(b) and A(c)-R¹(c), are those compounds wherein A is as defined above as A(c), R¹ is as defined above as R¹(a, b or c) and one of R³ or R⁴ is hydrogen (wherein R^{3,4a} refers to R³ as hydrogen and wherein R^{3,4b} refers to R⁴ as hydrogen). Such subgenera can be designated A(c)-R^{3,4a} and A(c)-R^{3,4b}, and sub-subgenera A(c)-R¹(a)-R^{3,4a}, A(c)-R¹(a)-R^{3,4b}, A(c)-R¹(b)-R^{3,4a}, A(c)-R¹(b)-R^{3,4b}, A(c)-R¹(c)-R^{3,4a} and A(c)-R¹(c)-R^{3,4b}.

[0062] Another embodiment of the invention of compounds of the formula A(c) compounds, including the subgenera A(c)-R¹(a), A(c)-R¹(b), A(c)-R¹(c), A(c)-R^{3,4a} and A(c)-R^{3,4b} and sub-subgenera A(c)-R¹(a)-R^{3,4a}, A(c)-R¹(a)-R^{3,4b}, A(c)-R¹(b)-R^{3,4a}, A(c)-R¹(b)-R^{3,4b}, A(c)-R¹(c)-R^{3,4a} and A(c)-R¹(c)-R^{3,4b}, are those compounds wherein two, three or four of X¹, X², X³ and X⁴ are hydrogen (wherein X¹ refers to two of X¹ - X⁴ as hydrogen, X^{1-4b} refers to three of X¹-X⁴ as hydrogen and X^{1-4c} refers to four of X¹ - X⁴ as hydrogen). Such subgenera can be designated A(c)-X^{1-4a}, A(c)-X^{1-4b}, A(c)-X^{1-4c}. Such sub-subgenera can be designated A(c)-R¹(a)-X^{1-4a}, A(c)-R¹(b)-X^{1-4a}, A(c)-R¹(c)-X^{1-4a}, A(c)-R^{3,4a}-X^{1-4a} and A(c)-R^{3,4b}-X^{1-4a}, A(c)-R¹(a)-X^{1-4b}, A(c)-R¹(b)-X^{1-4b}, A(c)-R¹(c)-X^{1-4b}, A(c)-R^{3,4a}-X^{1-4b} and A(c)-R^{3,4b}-X^{1-4b}, A(c)-R¹(a)-X^{1-4c}, A(c)-R¹(b)-X^{1-4c}, A(c)-R¹(c)-X^{1-4c}, A(c)-R^{3,4a}-X^{1-4c} and A(c)-R^{3,4b}-X^{1-4c}. Sub-sub-subgenera can be designated A(c)-R¹(a)-R^{3,4a}-X^{1-4a}, A(c)-R¹(a)-R^{3,4b}-X^{1-4a}, A(c)-R¹(b)-R^{3,4a}-X^{1-4a}, A(c)-R¹(b)-R^{3,4b}-X^{1-4a}, A(c)-R¹(c)-R^{3,4a}-X^{1-4a} and A(c)-R¹(c)-R^{3,4b}-X^{1-4a}, A(c)-R¹(a)-R^{3,4a}-X^{1-4b}, A(c)-R¹(a)-R^{3,4b}-X^{1-4b}, A(c)-R¹(b)-R^{3,4a}-X^{1-4b}, A(c)-R¹(b)-R^{3,4b}-X^{1-4b}, A(c)-R¹(c)-R^{3,4a}-X^{1-4b} and A(c)-R¹(c)-R^{3,4b}-X^{1-4b}, A(c)-R¹(a)-R^{3,4a}-X^{1-4c}, A(c)-R¹(a)-R^{3,4b}-X^{1-4c}, A(c)-R¹(b)-R^{3,4a}-X^{1-4c}, A(c)-R¹(b)-R^{3,4b}-X^{1-4c}, A(c)-R¹(c)-R^{3,4a}-X^{1-4c} and A(c)-R¹(c)-R^{3,4b}-X^{1-4c}.

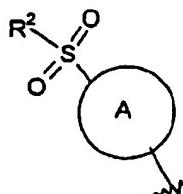
[0063] A group of compounds which is preferred among the A(c) Group compounds, including subgenera A(c)-R¹(a), A(c)-R¹(b), A(c)-R¹(c), are those compounds (designated subgenera A(c)-R^{3a}, and sub-subgenera A(c)-R¹(a)-R^{3a}, A(c)-R¹(b)-R^{3a}, A(c)-R¹(c)-R^{3a} including any preferences) wherein A is as defined above as A(c), R¹ is as defined above as R¹(a, b or c) and R³ is selected from hydrogen; halo; (C₁-C₄)alkyl optionally substituted with 1 to 3 halo; (C₁-C₄)alkoxy; (C₁-C₄)alkyl-O-C(=O)- and cyano (wherein said preferred R³ is referred to as R^{3a}).

[0064] Another group of compounds which is preferred among the A(c) Group of compounds, including subgenera A(c)-R¹(a), A(c)-R¹(b), A(c)-R¹(c), A(c)-R^{3a}, sub-subgenera A(c)-R¹(a)-R^{3a}, A(c)-R¹(b)-R^{3a}, A(c)-R¹(c)-R^{3a}, are those compounds (designated subgenera A(c)-R^{4a}, and sub-subgenera A(c)-R¹(a)-R^{4a}, A(c)-R¹(b)-R^{4a}, A(c)-R¹(c)-R^{4a}, A(c)-R¹(a)-R^{3a}-R^{4a}, A(c)-R¹(b)-R^{3a}-R^{4a}, A(c)-R¹(c)-R^{3a}-R^{4a}), wherein A is as defined above as A(c), R¹ is as defined above as R¹(a, b or c), R³ is defined above as R^{3a} and R⁴ is selected from hydrogen; halo; (C₁-C₄)alkyl optionally substituted with 1 to 3 halo; (C₁-C₄)alkoxy; (C₁-C₄)alkyl-O-C(=O)-and cyano (wherein said preferred R⁴ is R^{4a}).

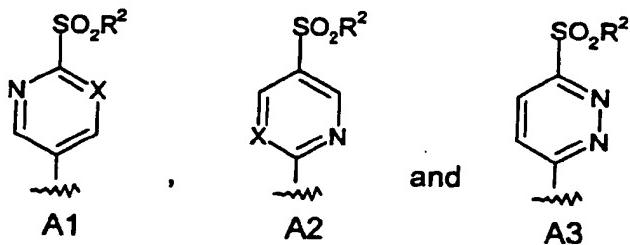
[0065] Another group of compounds which is preferred among each A(c) Group of compounds, including subgenera A(c)-R¹(a), A(c)-R¹(b), A(c)-R¹(c), A(c)-R^{3a}, A(c)-R^{4a}, sub-subgenera A(c)-R¹(a)-R^{3a}, A(c)-R¹(b)-R^{3a}, A(c)-R¹(c)-R^{3a}, A(c)-R¹(a)-R^{4a}, A(c)-R¹(b)-R^{4a}, A(c)-R¹(c)-R^{4a}, and A(c)-R^{3a}-R^{4a}, and sub-sub-subgenera A(c)-R¹(a)-R^{3a}-R^{4a}, A(c)-R¹(b)-R^{3a}-R^{4a}, A(c)-R¹(c)-R^{3a}-R^{4a}) are those compounds (designated subgenera A(c)-X^{1-4d} and sub-subgenera A(c)-R¹(a)-X^{1-4d}, A(c)-R¹(b)-X^{1-4d}, A(c)-R¹(c)-X^{1-4d}, A(c)-R^{3a}-X^{1-4d} and A(c)-R^{4a}-X^{1-4d} and sub-sub-subgenera A(c)-R¹(a)-R^{3a}-X^{1-4d}, A(c)-R¹(b)-R^{3a}-X^{1-4d}, A(c)-R¹(c)-R^{3a}-X^{1-4d}, A(c)-R¹(a)-R^{4a}-X^{1-4d}, A(c)-R¹(b)-R^{4a}-X^{1-4d}, A(c)-R¹(c)-R^{4a}-X^{1-4d}, A(c)-R^{3a}-R^{4a}-X^{1-4d} and sub-sub-sub-subgenera A(c)-R¹(a)-R^{3a}-R^{4a}-X^{1-4d}, A(c)-R¹(b)-R^{3a}-R^{4a}-X^{1-4d}, A(c)-R¹(c)-R^{3a}-R^{4a}-X^{1-4d}) wherein X¹ and X² are each independently selected from hydrogen; halo; (C₁-C₄)alkyl optionally substituted with 1 to 3 halo; cyano and (C₁-C₄)alkoxy (wherein X^{1-4d} refers to said preferred X¹ and X²).

[0066] A group of compounds which is preferred among each A(c) Group of compounds, including subgenera A(c)-R¹(a), A(c)-R¹(b), A(c)-R¹(c), A(c)-R^{3a}, A(c)-R^{4a}, sub-subgenera A(c)-R¹(a)-R^{3a}, A(c)-R¹(b)-R^{3a}, A(c)-R¹(c)-R^{3a}, A(c)-R¹(a)-R^{4a}, A(c)-R¹(b)-R^{4a}, A(c)-R¹(c)-R^{4a}, A(c)-R^{3a}-R^{4a}, and sub-sub-subgenera A(c)-R¹(a)-R^{3a}-R^{4a}, A(c)-R¹(b)-R^{3a}-R^{4a}, A(c)-R¹(c)-R^{3a}-R^{4a}) are those compounds (designated subgenera A(c)-X^{1-4e} and sub-subgenera A(c)-R¹(a)-X^{1-4e}, A(c)-R¹(b)-X^{1-4e}, A(c)-R¹(c)-X^{1-4e}, A(c)-R^{3a}-X^{1-4e} and A(c)-R^{4a}-X^{1-4e} and sub-sub-subgenera A(c)-R¹(a)-R^{3a}-X^{1-4e}, A(c)-R¹(b)-R^{3a}-X^{1-4e}, A(c)-R¹(c)-R^{3a}-X^{1-4e}, A(c)-R^{3a}-R^{4a}-X^{1-4e} and sub-sub-sub-subgenera A(c)-R¹(a)-R^{3a}-R^{4a}-X^{1-4e}, A(c)-R¹(b)-R^{3a}-R^{4a}-X^{1-4e}, A(c)-R¹(c)-R^{3a}-R^{4a}-X^{1-4e}) wherein X³ and X⁴ are each independently selected from hydrogen; halo; (C₁-C₄)alkyl optionally substituted with 1 to 3 halo; cyano and (C₁-C₄)alkoxy (wherein X^{1-4e} refers to said preferred X³ and X⁴).

[0067] A preferred group of compounds of this invention consists of those compounds of formula I, wherein



is selected from the group consisting of



10

wherein X is CH or N, and the heteroaryl moiety is unsubstituted, mono-, di- or tri-substituted with substituents independently selected from the group consisting of halo and (C₁-C₄)alkyl;

15 R¹ is heteroaryl selected from the group consisting of furyl, thiazolyl, oxazolyl, thienyl, tetrazolyl, triazolyl, imidazolyl, benzofuranyl and benzothienyl, wherein said heteroaryl is unsubstituted, mono-, di- or tri-substituted with substituents independently selected from the group consisting of halo and (C₁-C₄)alkyl;

R² is methyl;

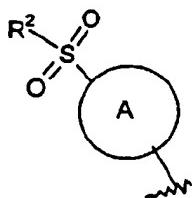
20 R³ and R⁴ are independently selected from the group consisting of hydrogen, halo and (C₁-C₄)alkyl optionally substituted with 1 to 3 halo; and

X¹, X², X³ and X⁴ are independently selected from the group consisting of hydrogen, halo, methyl, ethyl, methoxy, amino-C(=O)- and cyano.

[0068] A more preferred group of compounds of this invention consists of those compounds of formula I, wherein

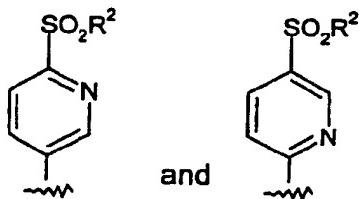
25

30



35 is selected from the group consisting of

35



45 wherein the heteroaryl moiety is optionally substituted with fluoro or methyl;

R¹ is selected from furyl, thiazolyl and oxazolyl;

R² is methyl;

50 R³ and R⁴ are each independently selected from hydrogen, chloro, fluoro, cyano, difluoromethyl and trifluoromethyl; and

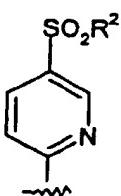
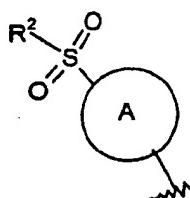
X¹, X², X³ and X⁴ are independently selected from hydrogen, chloro, fluoro, methyl and cyano.

[0069] Preferred compounds of this invention include

55 4-chloro-5-[3-methyl-4-(4-thiazolyl)phenyl]-1-[5-(2-methylsulfonyl)pyridyl]-3-trifluoromethyl-1 H-pyrazole;
5-(methylsulfonyl)-2-[5-[3-methyl-4-(1,3-thiazol-4-yl)phenyl]-3-trifluoromethyl-1 H-pyrazol-1 -yl]pyridine;
2-[5-[3-chloro-4-(1,3-thiazol-4-yl)phenyl]-3-trifluoromethyl-1 H-pyrazol-1 -yl]-5-(methylsulfonyl)pyridine;
5-[3-methyl-4-(1,3-thiazol-5-yl)phenyl]-1-[2-(5-methylsulfonyl)pyridyl]-3-trifluoromethyl-1 H-pyrazole;

5 [3-methyl-4-(4-oxazolyl)phenyl]-1-[2-(5-methylsulfonyl)pyridyl]-3-trifluoromethyl-1H-pyrazole;
 5-[3-methyl-4-(2-furyl)phenyl]-1-[2-(5-methylsulfonyl)pyridyl]-3-trifluoromethyl-1H-pyrazole;
 5-[3-methyl-4-(2-oxazolyl)phenyl]-1-[2-(5-methylsulfonyl)pyridyl]-3-trifluoromethyl-1H-pyrazole;
 2-[3-(difluoromethyl)-5-[3-methyl-4-(1,3-thiazol-4-yl)phenyl]-1H-pyrazol-1-yl]-5-(methylsulfonyl)-pyridine;
 2-[5-(3-chloro-4-furan-2-yl-phenyl)-3-trifluoromethyl-pyrazol-1-yl]-5-methanesulfonyl-pyridine;
 2-[5-(4-furan-2-yl-phenyl)-3-trifluoromethyl-pyrazol-1-yl]-5-methanesulfonyl-pyridine;
 5-[5-(3-chloro-4-furan-2-yl-phenyl)-3-trifluoromethyl-pyrazol-1-yl]-2-methanesulfonyl-pyridine;
 5-[5-(4-furan-2-yl-3-methyl-phenyl)-3-trifluoromethyl-pyrazol-1-yl]-2-methanesulfonyl-pyridine;
 2-furan-2-yl-5-[2-(5-methanesulfonyl-pyridin-2-yl)-5-trifluoromethyl-2H-pyrazol-3-yl]-benzonitrile;
 2-[5-(3-chloro-4-furan-2-yl-phenyl)-3-difluoromethyl-pyrazol-1-yl]-5-methanesulfonyl-pyridine;
 2-[5-(3-fluoro-4-furan-2-yl-phenyl)-3-trifluoromethyl-pyrazol-1-yl]-5-methanesulfonyl-pyridine;
 2-[3-difluoromethyl-5-(3-fluoro-4-furan-2-yl-phenyl)-pyrazol-1-yl]-5-methanesulfonyl-pyridine;
 5-methanesulfonyl-2-[5-(4-thiazol-2-yl-phenyl)-3-trifluoromethyl-pyrazol-1-yl]-pyridine; 5-[2-(5-methanesulfonyl-pyridin-2-yl)-5-trifluoromethyl-2H-pyrazol-3-yl]-2-thiazol-2-yl-benzonitrile;
 4-Fluoro-5-[4-(4-thiazolyl)phenyl]-1-[5-(2-methylsulfonyl)pyridyl]-3-trifluoromethyl-1H-pyrazole;
 2-[5-[2,5-dimethyl-4-(1,3-thiazol-4-yl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-1-yl]-5-(methylsulfonyl)pyridine;
 1-[5-(Methylsulfonyl)-2-pyridinyl]-5-[3-methyl-4-(1,3-thiazol-4-yl)phenyl]-1H-pyrazole-4-carbonitrile;
 5-[3-Methyl-4-(1,3-thiazol-2-yl)phenyl]-1-[2-(5-methylsulfonyl)pyridyl]-3-trifluoromethyl-1H-pyrazole;
 2-[5-[3-Fluoro-4-(1,3-thiazol-4-yl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-1-yl]-5-(methylsulfonyl)pyridine;
 2-Fluoro-3-(methylsulfonyl)-6-[5-[3-methyl-4-(1,3-thiazol-4-yl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridine; and
 2-Methyl-3-(methylsulfonyl)-6-[5-[3-methyl-4-(1,3-thiazol-4-yl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridine; or its salts.

25 [0070] An even more preferred compounds of this invention are those compounds of formula I wherein



45 R¹ is furyl, thiazolyl or oxazolyl; R² is methyl; R³ is di- or tri-fluoromethyl; R⁴ is hydrogen or chloro; X¹, X² and X⁴ are all hydrogen; and X² is hydrogen, chloro, fluoro, methyl or cyano.

[0071] Individual preferred compounds in the group are

50 4-chloro-5-[3-methyl-4-(4-thiazolyl)phenyl]-1-[5-(2-methylsulfonyl)pyridyl]-3-trifluoromethyl-1H-pyrazole;
 5-(methylsulfonyl)-2-[5-[3-methyl-4-(1,3-thiazol-4-yl)phenyl]-3-trifluoromethyl-1H-pyrazol-1-yl]pyridine;
 2-[5-[3-chloro-4-(1,3-thiazol-4-yl)phenyl]-3-trifluoromethyl-1H-pyrazol-1-yl]-5-(methylsulfonyl)pyridine;
 5-[3-methyl-4-(1,3-thiazol-5-yl)phenyl]-1-[2-(5-methylsulfonyl)pyridyl]-3-trifluoromethyl-1H-pyrazole;
 5-[3-methyl-4-(4-oxazolyl)phenyl]-1-[2-(5-methylsulfonyl)pyridyl]-3-trifluoromethyl-1H-pyrazole;
 5-[3-methyl-4-(2-furyl)phenyl]-1-[2-(5-methylsulfonyl)pyridyl]-3-trifluoromethyl-1H-pyrazole;
 5-[3-methyl-4-(2-oxazolyl)phenyl]-1-[2-(5-methylsulfonyl)pyridyl]-3-trifluoromethyl-1H-pyrazole;
 2-[3-(difluoromethyl)-5-[3-methyl-4-(1,3-thiazol-4-yl)phenyl]-1H-pyrazol-1-yl]-5-(methylsulfonyl)-pyridine;
 2-[5-(3-chloro-4-furan-2-yl-phenyl)-3-trifluoromethyl-pyrazol-1-yl]-5-methanesulfonyl-pyridine;
 2-[5-(4-Furan-2-yl-phenyl)-3-trifluoromethyl-pyrazol-1-yl]-5-methanesulfonyl-pyridine;
 5-[5-(3-Chloro-4-furan-2-yl-phenyl)-3-trifluoromethyl-pyrazol-1-yl]-2-methanesulfonyl-pyridine;

5-[(4-Furan-2-yl-3-methyl-phenyl)-3-trifluoromethyl-pyrazol-1-yl]-2-methanesulfonyl-pyridine;
 2-Furan-2-yl-5-[2-(5-methanesulfonyl-pyridin-2-yl)-5-trifluoromethyl-2H-pyrazol-3-yl]-benzonitrile;
 2-[5-(3-chloro-4-furan-2-yl-phenyl)-3-trifluoromethyl-pyrazol-1-yl]-5-methanesulfonyl-pyridine;
 2-[5-(3-fluoro-4-furan-2-yl-phenyl)-3-trifluoromethyl-pyrazol-1-yl]-5-methanesulfonyl-pyridine;
 2-[3-Difluoromethyl-5-(3-fluoro-4-furan-2-yl-phenyl)-pyrazol-1-yl]-5-methanesulfonyl-pyridine;
 5-Methanesulfonyl-2-[5-(4-thiazol-2-yl-phenyl)-3-trifluoromethyl-pyrazol-1-yl]-pyridine; and
 5-[2-(5-Methanesulfonyl-pyridin-2-yl)-5-trifluoromethyl-2H-pyrazol-3-yl]-2-thiazol-2-yl-benzonitrile; or its salts.

[0072] This invention also relates to method of treating or preventing diseases or conditions in a mammal, comprising administering a compound of formula I to the mammal, wherein the disease or condition is selected from the group consisting of diseases or conditions in which prostaglandins are implicated as pathogens, pain, fever, inflammation, rheumatic fever, symptoms associated with influenza and other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis including rheumatoid arthritis, degenerative joint disease or osteoarthritis, gout and ankylosing spondylitis, bursitis, burns, injuries following surgical and dental procedures, disease or conditions associated with cellular neoplastic transformations and metastatic tumor growth, cancer, colorectal cancer, breast and skin cancer, familiar adenomatous polyposis, cyclooxygenase-mediated proliferation disorders, cyclooxygenase-mediated proliferation disorders in diabetic retinopathy and tumor angiogenesis, prostanoid-induced smooth muscle contraction mediated by synthesis of contractile prostanoids, dysmenorrhea, premature labor, asthma, eosinophil related disorders, neurodegenerative diseases, Alzheimer's and Parkinson's disease, bone loss, osteoarthritis, peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis, recurrent of gastrointestinal lesions, gastrointestinal bleeding, coagulation, anemia, hypoprothrombinemia, haemophilia, bleeding problems; kidney disease and conditions prior to surgery of taking of anticoagulants.

[0073] This Invention relates to a method for treating or preventing a disease or condition wherein the disease or condition is selected from the group consisting of diseases or conditions in which prostaglandins are implicated as pathogens, pain, fever, inflammation, rheumatic fever, symptoms associated with influenza and other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis including rheumatoid arthritis, degenerative joint disease or osteoarthritis, gout and ankylosing spondylitis, bursitis, burns, injuries following surgical and dental procedures, disease or conditions associated with cellular neoplastic transformations and metastatic tumor growth, cancer, colorectal cancer, breast and skin cancer, familiar adenomatous polyposis, cyclooxygenase-mediated proliferation disorders, cyclooxygenase-mediated proliferation disorders in diabetic retinopathy and tumor angiogenesis, prostanoid-induced smooth muscle contraction mediated by synthesis of contractile prostanoids, dysmenorrhea, premature labor, asthma, eosinophil related disorders, neurodegenerative diseases, Alzheimer's and Parkinson's disease, bone loss, osteoarthritis, peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis, recurrent of gastrointestinal lesions, gastrointestinal bleeding, coagulation, anemia, hypoprothrombinemia, haemophilia, bleeding problems; kidney disease and conditions prior to surgery of taking of anticoagulants.

[0074] This Invention also relates to a pharmaceutical composition for treating or preventing a disease or condition selected from the group consisting of diseases or conditions in which prostaglandins are implicated as pathogens, pain, fever, inflammation, rheumatic fever, symptoms associated with influenza and other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis including rheumatoid arthritis, degenerative joint disease or osteoarthritis, gout and ankylosing spondylitis, bursitis, burns, injuries following surgical and dental procedures, disease or conditions associated with cellular neoplastic transformations and metastatic tumor growth, cancer, colorectal cancer, breast and skin cancer, familiar adenomatous polyposis, cyclooxygenase-mediated proliferation disorders, cyclooxygenase-mediated proliferation disorders in diabetic retinopathy and tumor angiogenesis, prostanoid-induced smooth muscle contraction mediated by synthesis of contractile prostanoids, dysmenorrhea, premature labor, asthma, eosinophil related disorders, neurodegenerative diseases, Alzheimer's and Parkinson's disease, bone loss, osteoarthritis, peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis, recurrent of gastrointestinal lesions, gastrointestinal bleeding, coagulation, anemia, hypoprothrombinemia, haemophilia, bleeding problems; kidney disease and conditions prior to surgery of taking of anti-coagulants.

General Synthesis

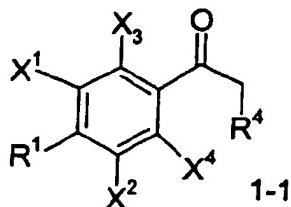
[0075] Compounds of general formula (I) may be prepared by a variety of synthetic routes. Representative preparation procedures are outlined below. Unless otherwise indicated, A, R¹, R², R³, R⁴, X¹, X², X³ and X⁴ are as defined herein above.

[0076] In a desired reaction step of the processes described hereafter, NH or hydroxy protections and removals of the protecting groups used may be carried out according to known procedures such as those described in Protective

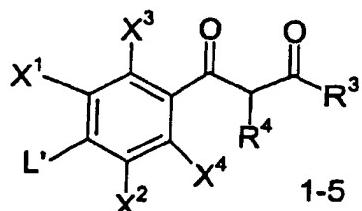
Groups in Organic Synthesis edited by T. W. Green *et al.* (John Wiley & Sons, 1991). Isolated hydroxy groups can generally be protected as ethers including t-butyldimethylsilyl ethers, acetals and sters. In general, benzyl-type protecting groups are removed by hydrogenolysis, silyl esters by reaction with fluoride ions or under slightly acidic conditions and several 2-substituted thyl ethers can be cleaved by beta-elimination reactions.

5 [0077] Scheme 1 illustrates preparation methods of compounds of formula I through pyrazole ring formation.

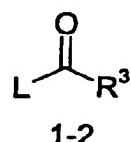
SCHEME 1

ROUTE 1

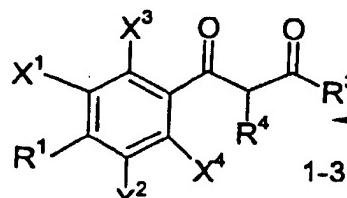
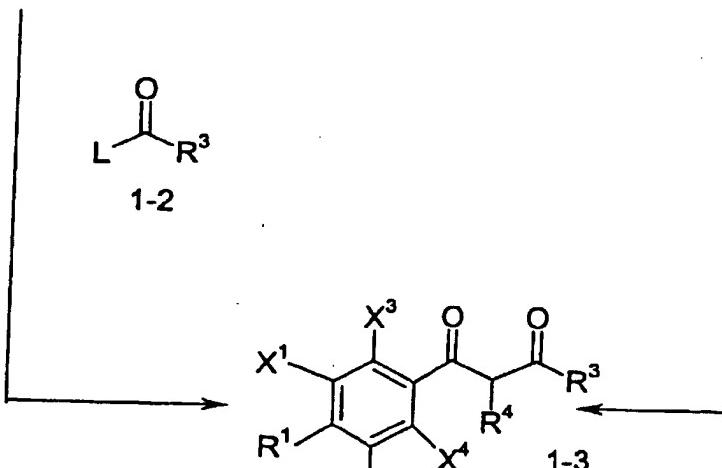
1-1

ROUTE 2

1-5



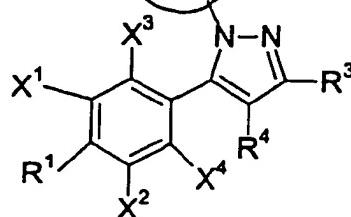
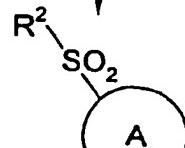
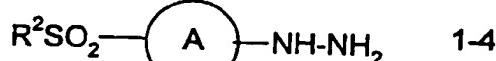
1-2



1-3



1-6



(I)

Route 1 (Acylation and Pyrazole-ring Formation):

[0078] Referring to Route 1, a compound of the formula I may be prepared by reacting a diketone compound of formula 1-3 with a hydrazine compound of the formula 1-4 in a reaction inert solvent. Suitable solvents used in this reaction include alcohols such as ethanol, trifluoroethanol, methanol, propanol, isopropanol and butanol; dimethyl sulfoxide (DMSO); N,N-dimethylformamide (DMF); acetic acid; N,N-dimethylacetamide (DMA) and N-methyl-2-pyrrolidinone (NMP). Preferred solvents used in this reaction are methanol, ethanol and acetic acid.

This reaction may be conducted in the presence of a stoichiometric or catalytic amount of acid such as hydrochloric acid, acetic acid, trifluoroacetic acid, p-toluenesulfonic acid or sulfuric acid, preferably acetic acid. Alternatively, a compound of formula 1-4 may be subjected to the reaction as an acid addition salt such as hydrochloride. This reaction is generally carried out at a temperature from about 0°C to about 140°C, preferably at about the reflux temperature of the solvent for from about 2 to about 20 hours.

[0079] A compound of formula 1-3 is prepared from a compound of formula 1-1 by reaction with a compound of the formula 1-2 wherein L is a suitable leaving group in the presence of a suitable base and a reaction inert solvent.

Compounds of formula 1-2 may be subjected to the reaction as esters; or ester equivalents such as acylimidazole; dialkylamide; halides; thioesters or acid anhydride. A compound of formula 1-2 is preferably used in this reaction as an acylimidazole or ester. Suitable bases used in this reaction include n-butyl lithium, potassium carbonate (K_2CO_3), sodium carbonate (Na_2CO_3), cesium carbonate (Cs_2CO_3), sodium hydride (NaH), sodium methoxide, potassium-*tert*-butoxide, lithium diisopropylamide (LDA), pyrrolidine, piperidine, lithium 1,1,1,3,3-hexamethyldisilazane ((Me_3Si_2)₂NLi) and the like. A preferred base is sodium methoxide. This reaction can be carried out in a solvent such as a di-(alkyl)ether (preferred is methyl *tert*-butyl ether), tetrahydrofuran (THF), dimethoxyethane (DME), 1,4-dioxane, methanol, dichloromethane, dimethylformamide (DMF), dimethylacetamide (DMA), or DMSO. Reaction temperature ranges from about -100° to about 150°C preferably from about 0°C to about 50°C, more preferably at about room temperature (i.e., from about 20°C to about 25°C) for from about 0.5 to 20 hours.

Route 2 (R¹-moiety Introduction and Pyrazole-ring Formation):

[0080] As illustrated in Route 2, a compound of formula I may also be prepared by (1) a cross-coupling-reaction of a compound of formula 1-5, wherein L' is a suitable leaving group, with a compound of formula 1-6 followed by (2) pyrazole ring formation with a hydrazine compound of formula 1-4 as described herein above. In the cross-coupling reaction, a compound of formula 1-5 may be coupled with compounds of formula 1-6 under reaction conditions known to those skilled in the art. Typical compounds of formula 1-6 used in this reaction include boronic acid (so called Suzuki reaction), zinc halide (so called Negishi reaction), and tin (IV) derivatives (so called Stille reaction) and the like (for examples refer to Tetrahedron, Vol. 54, pp. 263-303, 1998; S. P. Stanforth). A suitable leaving group L' includes halogen, such as chloro, bromo or iodo, preferably iodo, or trifluorosulfonyloxy ($CF_3SO_3^-$).

[0081] When a compound of formula 1-6 is a boronic acid derivative the reaction is typically run in the presence of a suitable base and a palladium catalyst. A suitable base includes, but is not limited to, potassium hydroxide, thallium hydroxide, sodium or potassium bicarbonate, or an alkyl amine such as, but not limited to, triethylamine. Palladium catalysts typically employed include, for example, tetrakis(triphenylphosphine)palladium and dichlorobis(triphenylphosphine)palladium. Suitable solvents used in this reaction include, but is not limited to, benzene, toluene, dimethoxyethane (DME), 1,4-dioxane and dimethylformamide (DMF), preferably DME. Alternatively, the reaction may be conducted in biphasic media, for example, DME/water or 1,4-dioxane/water, preferably DME/water. The reaction is usually carried out at reflux temperature of solvent, however, lower or higher temperatures may be employed. Reaction time is typically for from 10 minutes to several days, usually for from 30 minutes to 15 hours.

[0082] When a compound of formula 1-6 is a zinc halide derivative the reaction is typically run in a suitable reaction inert solvent in the presence of a palladium or nickel catalyst. Suitable catalysts include, for example, tetrakis(triphenylphosphine)palladium, tetrakis(triphenylphosphine)nickel, dichlorobis(triphenylphosphine)palladium, dichlorobis(1,1-bis(diphenylphosphino)ferrocene)palladium, or dichlorobis(1,4-bis(diphenylphosphino)butane)palladium. Suitable solvents used in this reaction include, but is not limited to, tetrahydrofuran (THF), diethylether and dimethoxyethane (DME), preferably THF. The reaction is usually carried out at reflux temperature of solvent, however, lower or higher temperatures may be employed. Reaction time is typically for from about 10 minutes to several days, usually for from about 30 minutes to 15 hours.

[0083] When a compound of formula 1-6 is a tin (IV) derivative, for example, Me_3Sn-R^1 or Bu_3Sn-R^1 , the reaction is typically run in a suitable reaction inert solvent in the presence a palladium catalyst. Palladium catalysts typically employed include, for example, tetrakis(triphenylphosphine)palladium and dichlorobis(triphenylphosphine)palladium. If necessary, a co-catalyst such as lithium chloride, ammonium hydroxide or copper(1) bromide may be used. Suitable solvents used in this reaction include, but is not limited to, benzene, toluene, dimethoxyethane (DME), 1,4-dioxane, tetrahydrofuran (THF) and dimethylformamide (DMF), preferably DME or 1,4-dioxane. The reaction is usually carried

out at reflux temp. rature of solvent, however, lower or higher temp. ratures may be employed. Reaction time is typically from 10 minutes to several days, usually for from 30 minutes to 15 hours.

[0084] Alternatively, compounds of formula I-3 may also be prepared by heteroaryl-ring formation on a corresponding acyl phenol, acyl halobenzene or N-formylmethylbenzamide compounds and acylation at para-position on the phenyl ring. The ring formations include (a) thiazole ring formation; (b) oxazole ring formation; (c) triazole ring formation; and (d) imidazole ring formation.

5 (a) Thiazole ring formation:

10 The thiazole ring formation can typically be carried out by first introducing a leaving group such as halo into the acyl moiety then reacting the compound thus obtained with either phosphorus pentasulfide in the presence of formamide, or thioacetamide. These reactions can be carried out in a reaction inert solvent such as dioxane under reflux.

15 (b) Oxazole ring formation:

15 The oxazole ring formation can typically be carried out by treating a 2-halo-1-phenyl-butanone compound in the presence of ammonium formate in formic acid under reflux. The oxazole ring formation may also be carried out treating an N-formylmethylbenzamide compound in the presence of triphenylphosphine, iodine and triethylamine.

20 (c) Triazole ring formation:

20 Compounds of formula I-1 wherein R¹ is triazolyl may be prepared by reacting a cyano benzene compound with trimethylsilyldiazomethane in the presence of n-butyl lithium in a mixture of hexane and diethyl ether at about 0°C.

25 (d) Imidazole ring formation:

25 Compounds of formula I wherein R¹ is imidazolyl may be prepared by reacting a known halomethyl-carbonyl-benzene compound (e.g., those compounds described in *Justus Liebigs Ann. Chem.*, 1941, 546, 277 by Herbert) with formamide in water at about 140°C.

[0085] The latter acylation may be carried out by methods known to those skilled in the art or methods illustrated in Route 1 of Scheme 1.

[0086] Starting materials used in the processes in Scheme 1 are known compounds or readily prepared by methods known to those skilled in the art (e.g., *Collection Czechoslov. Chem. Common.* Vol. 37, p. 1721, 1972 by J. Vavrlna et al.).

[0087] Scheme 2 illustrates an alternate method for preparing compounds of formula I.

35

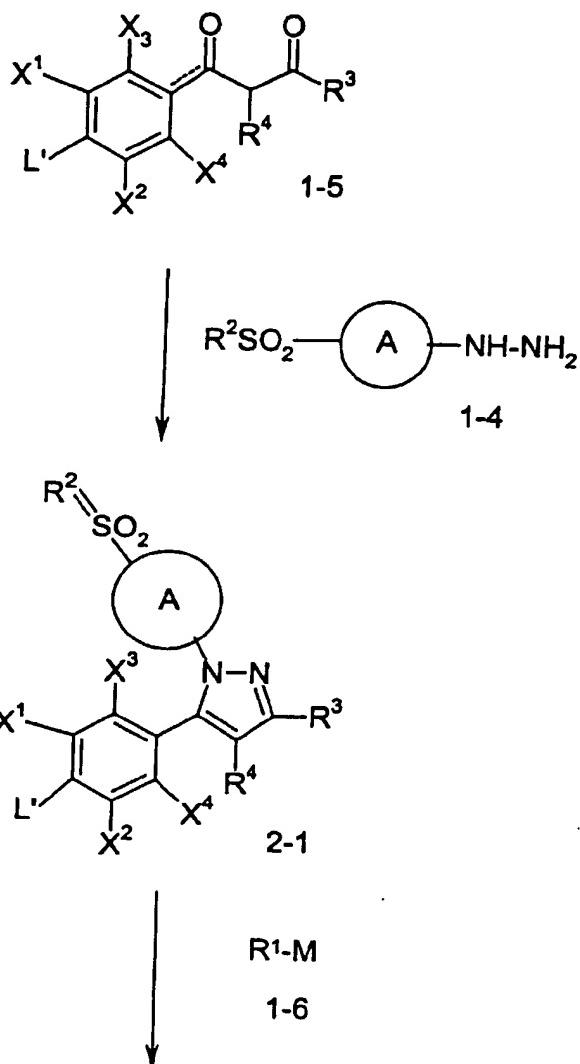
40

45

50

55

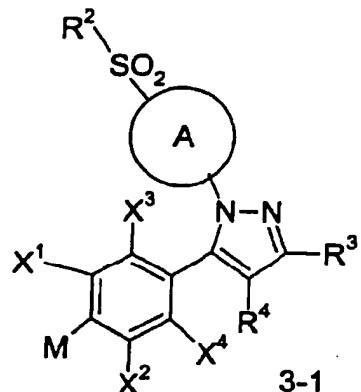
SCHEME 2



Thus, a compound of formula I may also be prepared by a cross-coupling reaction of a compound of formula 2-1, wherein L' is a suitable leaving group, with a compound of formula 1-6. In the cross-coupling reaction, a compound of formula 2-1 may be coupled with compounds of formula 1-6 under reaction conditions known to those skilled in the art. Typical compounds of formula 1-6 used in this reaction include boronic acid (so called Suzuki reaction), zinc halide (so called Negishi reaction), and tin (IV) derivatives (so called Stille reaction) and the like (for examples refer to Tetrahedron, Vol. 54, pp. 263-303, 1998; S. P. Stanforth). A suitable leaving group L' includes halogen, such as chloro, bromo or iodo, preferably iodo, or trifluorosulfonyloxy (CF_3SO_3^-). Procedures typically employed are analogous to those described herein before in route 2 (Scheme 1).

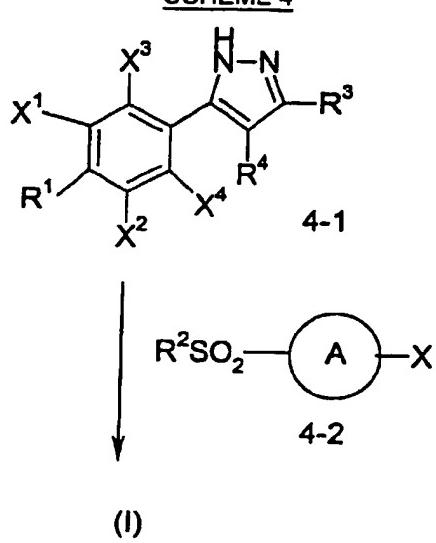
[0088] A compound of formula 2-1 is readily prepared from a compound of formula 1-5 and a compound of formula 1-4 according to analogous procedures illustrated in Scheme 1 described hereinbefore.

[0089] In another embodiment, compounds of formula I may be prepared as illustrated in Scheme 2 according to analogous procedures illustrated in Scheme 1 described herein before.

SCHEME 3

30 Thus, a compound of formula I may also be prepared by a cross-coupling reaction of a compound of formula 3-1, wherein M is a boronic acid (e.g., -B(OH)₂), a zinc halide (e.g., -ZnCl) or a tin (IV) (e.g., -Sn(n-Bu)₃) derivative, with a compound of formula 3-2, wherein L¹ is a suitable leaving group, such as chloro, bromo or iodo, preferably iodo, or trifluorosulfonyloxy (CF₃SO₃⁻). In the cross-coupling reaction, a compound of formula 3-1 may be coupled with compounds of formula 3-2 under reaction conditions known to those skilled in the art. Compounds of formula 3-1 are readily prepared from compounds of formula 2-1 (Scheme 2) by standard metal-halogen exchange reactions known to those skilled in the art.

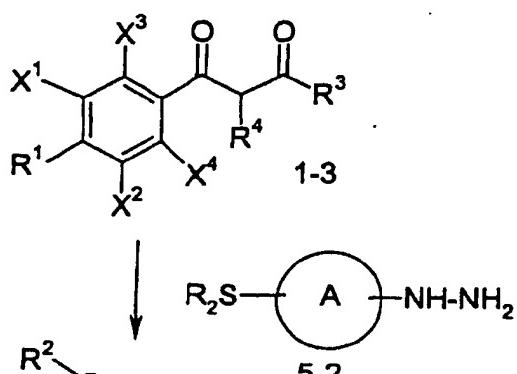
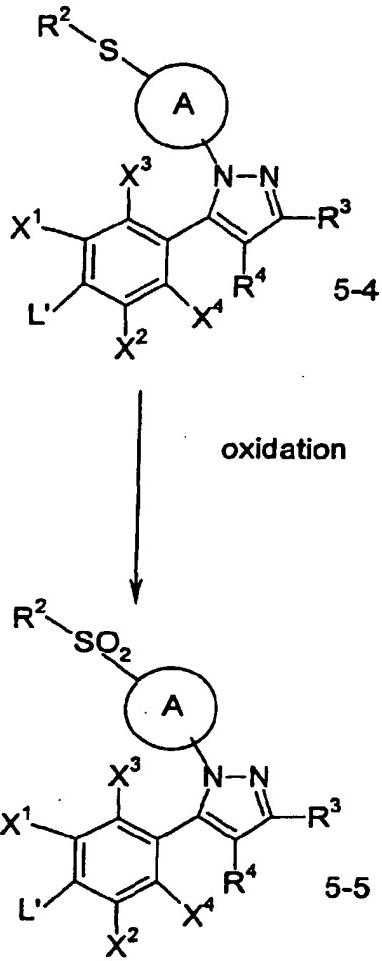
35 [0090] Alternatively, compounds of formula I may be prepared as illustrated in Scheme 4.

SCHEME 4

[0091] According to Scheme 4, a pyrazole compound of formula 4-1 may be coupled with a compound of formula 4-2 wherein X is halo, for example, fluoro, bromo or iodo, to yield a compound of formula I. The coupling reaction is usually carried out in the presence of a suitable base such as n-butyllithium (n-BuLi) sodium hydride, potassium carbonate, cesium carbonate, potassium tert-butoxide, triethylamine, pyridine, or the like. A suitable reaction inert solvent includes, but is not limited to, tetrahydrofuran (THF), dimethoxyethane (DME), dimethyl sulfoxide (DMSO), dimethylformamide (DMF) or toluene. The reaction is usually carried out at reflux temperature of solvent, however, lower or higher temperatures may be employed. Reaction time is typically for from 10 minutes to several days, usually for from 30 minutes to 15 hours. If desired, a catalyst such as copper (II) oxide or copper (II) bromide may be added to the reaction mixture. Compounds of formula 4-1 may be prepared according to similar procedures illustrated in Scheme 1 described herein before.

[0092] Compounds of formula I may also be prepared according to the procedures illustrated in Scheme 5 through oxidation.

15

SCHEME 5ROUTE 1ROUTE 2

50

oxidation**(I)**Route 1 (Pyrazole-ring Formation and Oxidation):

[0093] According to Route 1, a sulfide compound of formula 5-1 may be oxidized to the compound of formula I using a suitable oxidizing reagent in a reaction inert solvent. This reaction is usually carried out at a temperature from -20°C

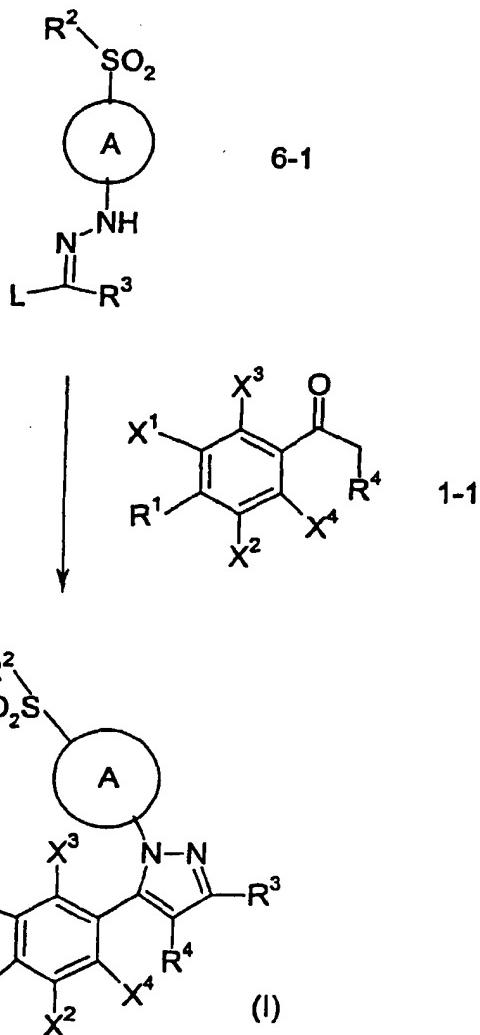
to the reflux temperature of the reaction mixture for from about 10 minutes to about 30 hours. Preferably, the reaction may be carried out at a temperature in the range of 0° to 50°C for from about 1 to 20 hours. Suitable oxidizing reagents include mCPBA (m-chloroperoxybenzoic acid), peracetic acid, hydrogen peroxide and oxone. Preferred is mCPBA. Compounds of formula 5-1 may be prepared according to the procedures of Scheme 1 except that a sulfide hydrazine compound of formula 5-2 is used instead of a sulfonyl hydrazine compound of formula 1-4.

Route 2 (Oxidation and R¹-moiety Introduction):

[0094] According to Route 2, compounds of formula 5-4 may be oxidized to compounds of formula 5-5 (2-1) and then converted to compounds of formula I by introducing R¹ group. The oxidation of compounds of formula 5-4 may be carried out according to the similar procedures as illustrated in Route 1 (Scheme 5). Compounds of formula 5-5 (2-1) may be converted to compounds of formula I by coupling reaction with a desired coupling reagent comprising R¹ group according to procedures known to those skilled in the art or similar procedures as illustrated in Scheme 1 and the discussed herein before.

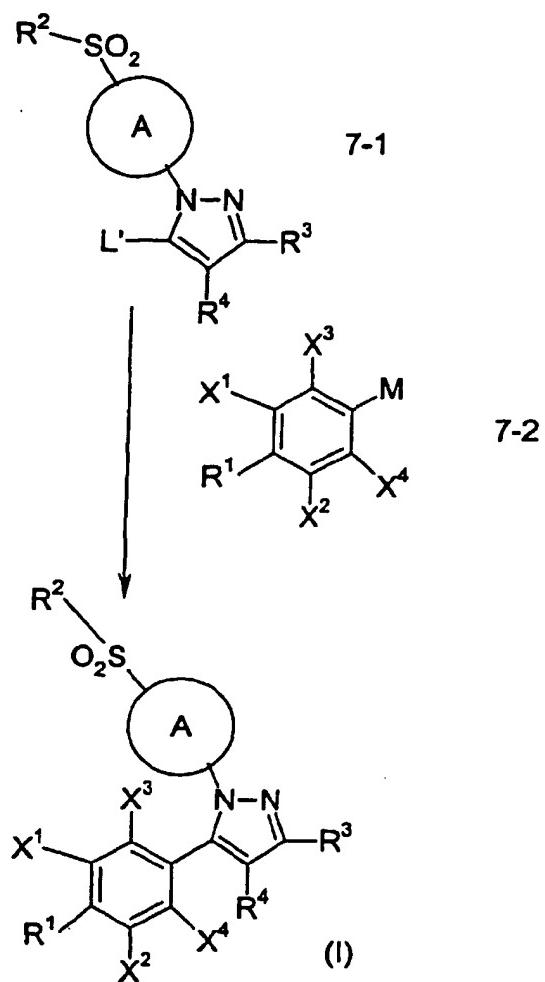
15

SCHEME 6

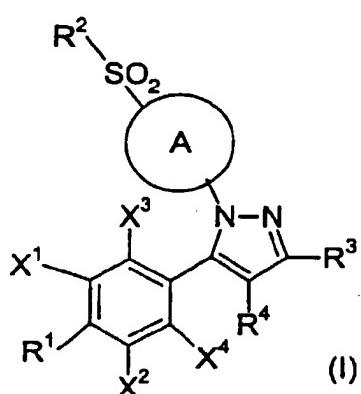
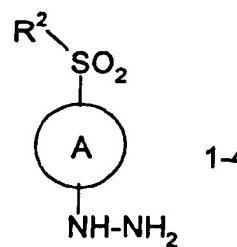
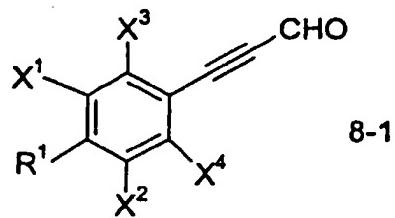


Scheme 6 illustrates another preparation methods of compounds of formula I (Heterocycles, 1990, 31, 1041).

SCHEME 7



40 Referring to Scheme 7, a compound of formula I may also be prepared by a coupling reaction of compound of formula 7-1 and a compound of formula 7-2 under similar conditions illustrated in Scheme 1 or 2.

SCHEME 8

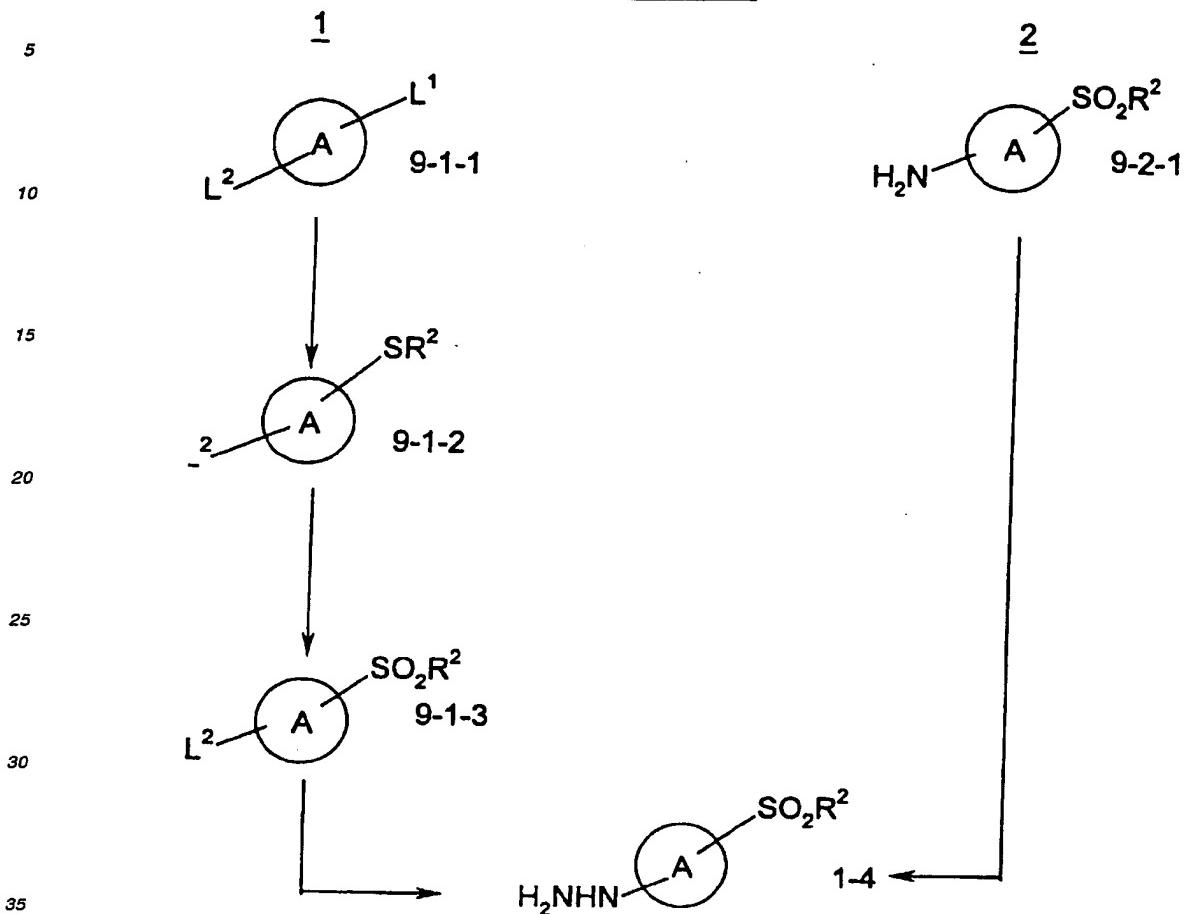
Formation of Hydrazine Compounds of Formula 4-1:

40 [0095] Scheme 9 illustrates preparation methods of hydrazine compounds formula 4-1 which can be used in the preparation process illustrated in Scheme 1.

45

50

55

SCHEME 9

Route 1 (Thioalkylation and Oxidation):

[0096] As illustrated in Route 1, compounds of formula 1-4 can be prepared by subjecting a compound of the formula 9-1-1 wherein L^1 and L^2 are leaving groups to thioalkylation, oxidation and reaction with hydrazine or anhydrous hydrazine. Suitable leaving groups of the compounds used in this reaction are halo. In this process, compounds of the formula 1-4 are prepared from compounds of the formula 9-1-3 by reaction with hydrazine or anhydrous hydrazine in the presence of a polar solvent. Suitable solvents used in this reaction include alcohol, such as ethanol, methanol, propanol or butanol; dimethyl sulfoxide (DMSO), N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA) or N-methyl-2-pyrrolidinone (NMP), preferably an alcohol, most preferably ethanol. This reaction is generally carried out at a temperature from about 0°C to about 140°C, preferably at about the reflux temperature of the polar solvent. Preferably the product is isolated as a salt, such as a hydrochloride salt. The reaction time ranges from about 1 hour to about 1 day. The compound of formula 9-1-3 is prepared from a compound of formula 9-1-2 by reaction with an oxidizing reagent in the presence of a solvent. Suitable oxidants include meta-chloroperbenzoic acid, hydrogen peroxide, sodium perborate, or Oxone® (Oxone® is preferred). Suitable solvents or solvent mixtures used in this reaction include methanol-water, dioxane-water, tetrahydrofuran-water, methylene chloride, or chloroform, preferably methanol-water. Suitable temperatures for the aforesaid reaction range from about 0°C to about 60°C, preferably the temperature may range from about 20°C to about 25°C (i.e. room temperature). The reaction is complete within about 0.5 hours to about 24 hours, preferably about 16 hours. The compound of the formula 9-1-2 is prepared from a compound of formula 9-1-1 by nucleophilic substitution reaction using a sulfur nucleophilic reagent such as alkylthiol, dialkyldisulfide, sodium alkylsulfinate, sodium thioalkoxide or potassium thioalkoxide, in the presence or absence of a base in a polar solvent. Suitable bases used in this reaction include sodium hydroxide, triethylamine; alkylolithiums such as n-butyllithium, sec-butyllithium, and *tert*-butyllithium; and lithium diisopropylamide, and suitable solvents include ethers such as dimeth-

EP 1 104 759 A1

ylether; alkanols such as methanol, ethanol and *tert*-butanol; a mixture of an alkanol and water; THF; benzene; toluene; xylene; DMF; DMSO; dioxane; and 1,2-dimethoxyethane. This reaction is generally carried out at a temperature from about -78°C to 200°C for from about 1 minute to 3 days.

5 Route 2 (Hydrazine formation):

[0097] Referring to Route 2, compound of the formula 1-4 may be prepared by reaction of a compound the formula 9-2-1 with a suitable reagent followed by reduction in an inert solvent or by catalytic hydrogenation. Typical reagents used in the first step include sodium nitrite in an aqueous medium (e.g., hydrochloric acid in water); nitrosyl chloride, nitrogen oxides and nitrile ethers. This reaction is typically carried out at about 0°C for from about 1 minute to about 10 hours. Suitable reducing agents used in the subsequent reduction include zinc powder-acetic acid, metal halides such as TiCl₃ or SnCl₂, sodium-ethanol, sodium-aqueous ammonia, lithium aluminum hydride and the like. Catalytic hydrogenation may be carried out using a catalyst such as palladium on carbon (Pd/C), palladium on barium sulfate (Pd/BaSO₄), platinum on carbon (Pt/C), or tris(triphenylphosphine) rhodium chloride (Wilkinson's catalyst), in an appropriate solvent such as methanol, ethanol, THF, dioxane or ethyl acetate, at a pressure from about 1 to about 5 atmospheres and a temperature from about 10°C to about 60°C. The following conditions are preferred: Pd on carbon, methanol at 25°C and 50 psi of hydrogen gas pressure. This method also provides for introduction of hydrogen isotopes (i.e., deuterium, or tritium) by replacing ¹H₂ with ²H₂ or ³H₂ in the above procedure. Compounds of formula 1-4 thus obtained may be isolated as an acid addition salt such as the hydrochloride salt. Compounds of formula 9-1-1 and 9-2-1 are commercially available or can be prepared by methods well known to those of ordinary skill in the art (e.g., F. Walker et al., J. Chem. Soc. 1939, 1948).

[0098] Triazine compounds of formula 1-4 can be prepared according to the methods illustrated in Scheme 10. In Scheme 10, triazine compounds of formula 1-4 are represented as compounds of formula 10-5.

25

30

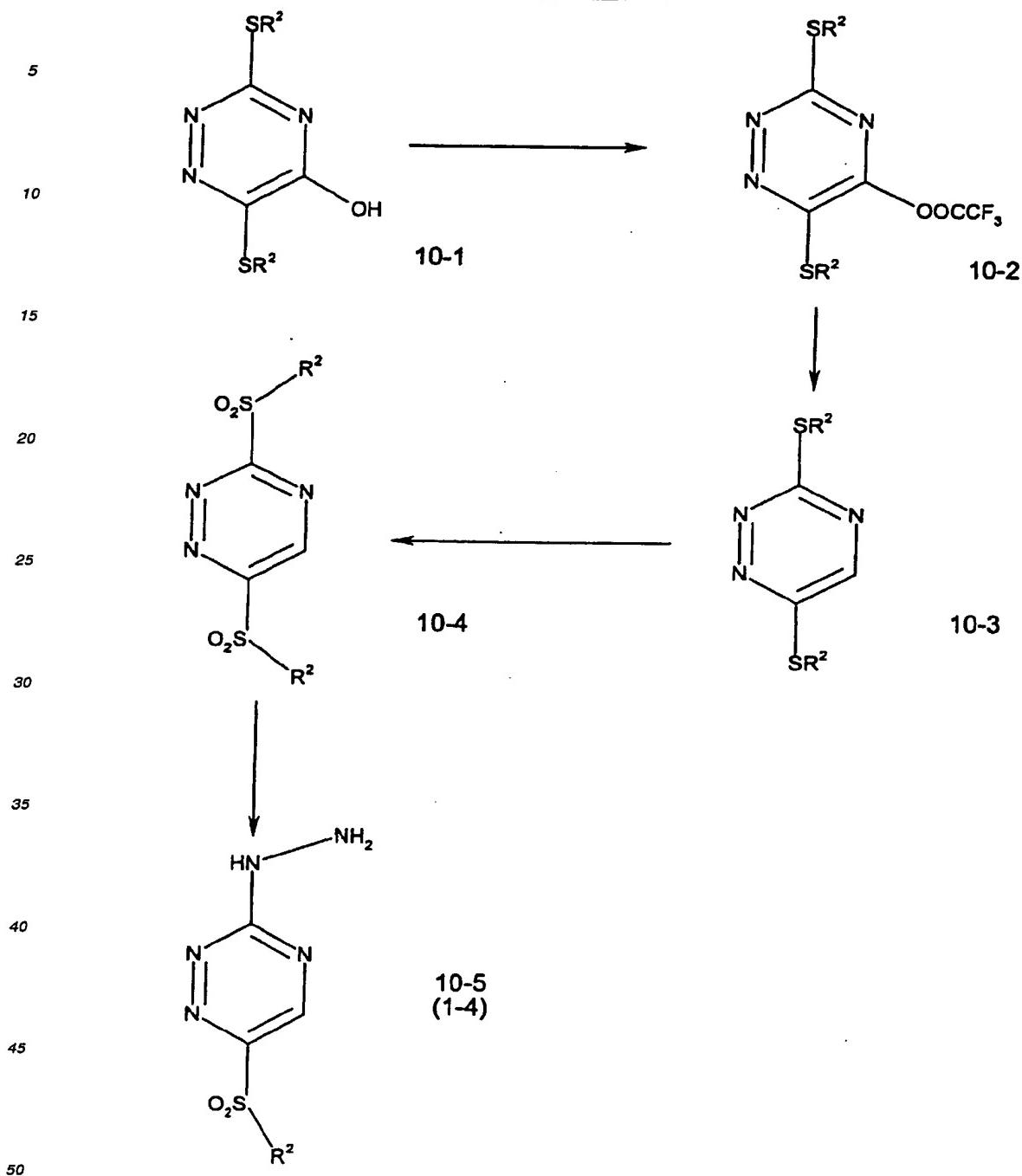
35

40

45

50

55

SCHEME 10

Scheme 10 illustrates preparation methods of compounds of formula 10-5 from compounds of formula 10-1 by substitution reaction with triflate to compounds of formula 10-2; reduction to compounds of formula 10-3; oxidation to compounds of formula 10-4; and substitution reaction with hydrazine. Substitution reaction of compounds of formula 10-1 with triflate can be carried out using triflic anhydride in the presence of pyridine. Reduction of compounds of formula 10-2 may be carried out using a suitable reducing reagent such as sodium borohydride or lithium aluminum hydride. Oxidation of compounds of formula 10-3 may be carried out by using mCPBA or Oxone as described in Scheme 5 and its discussion. Reaction with compounds of formula 10-4 and hydrazine can be carried out in an alcoholic solvent.

EP 1 104 759 A1

Compounds of formula 10-5 thus obtained may be subjected to reactions with dike tone compounds as illustrated in Scheme 1 using a acid catalyst such as sulfuric acid in 2,2,2-trifluoroethanol under reflux to yield compounds of formula 1. In the process illustrated in Scheme 10, halogen can be also introduced to compounds of formula 10-2 instead of triflate under known conditions such as chlorination using phosphoryl oxychloride. Compounds of formula 10-1 may be prepared by known procedures described in literature such as *J. Org. Chem.*, Vol. 63, p. 6329, 1998.
 [0099] Scheme 11 illustrates preparation methods for synthesizing compounds of formula 11-3, which can be subjected to reactions illustrated in Scheme 9.

10

SCHEME 11

15

20

25

30

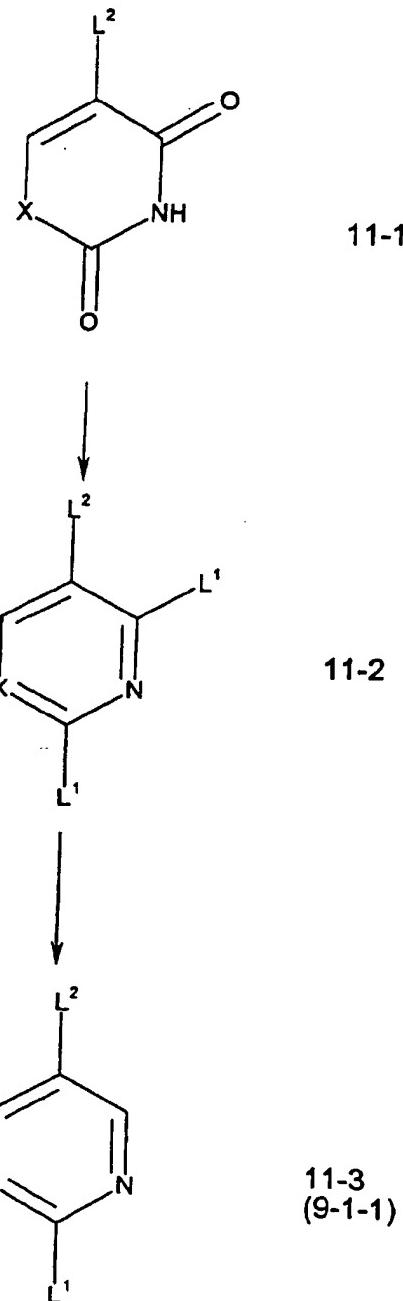
35

40

45

50

55



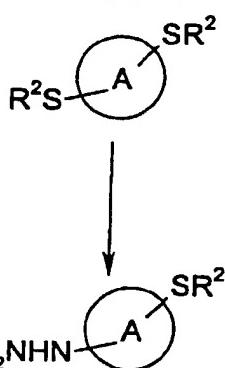
Referring to Schem 11, a dicarbonyl compound of formula 11-1, wh rein X is NH (i.e., pyrimidine compounds) or CH (i.e., pyridine compounds) and L² is a leaving group, may be subjected to substitution r action to introduce L¹ to give the compound of formula 11-2 followed by reduction to give the compound of formula 11-3. Typical leaving groups L¹ and L² are halo, which can be introduc d by halog nation according to methods known for thos skilled in the art. For example, chlorination of a compound of formula 11-1 can be carried out using a chlorinating reagent such as an excess amount of phosphoryl chloride in the presence or absence of a base such as N,N-diethylaniline. This reaction can typically be carried out under reflux for from about 30 minutes to about 10 hours. The subsequent reduction of compounds of formula 11-2 may be carried out using a reducing reagent such as a metal catalyst in the presence of a base in a reaction inert solvent according to known methods in the art. For example, this reaction can typically be carried out using zinc powder in the presence of ammonia in a reaction inert solvent such as benzene at about room temperature for from about 1 hour to about 1 day. Then, compounds of formula 11-3 thus obtained can be subjected to the reactions illustrated in Scheme 9.

[0100] Scheme 12 illustrates the other hydrazine preparation methods.

15

SCHEME 12

20



25

30

The starting materials in the aforementioned general syntheses may be obtained by conventional methods known to those skilled in the art. The preparation of such starting materials is described within the accompanying non-limiting examples which are provided for the purpose of illustration only. Alternatively, requisite starting materials may be obtained by analogous procedures, or modifications thereof, to those described hereinafter.

[0101] In each reaction described above, unless indicated otherwise, the reaction pressure is not critical. Generally, the reactions will be conducted at a pressure of about one to about three atmospheres, preferably at ambient pressure (about one atmosphere).

[0102] The starting materials in the aforementioned general syntheses may be obtained by conventional methods known to those skilled in the art. The preparation of such starting materials is described within the accompanying non-limiting examples which are provided for the purpose of illustration only. Alternatively, requisite starting materials may be obtained by analogous procedures, or modifications thereof, to those described hereinafter.

[0103] The products which are addressed in the aforementioned general syntheses and illustrated in the experimental examples described herein after may be isolated by standard methods and purification can be achieved by conventional means known to those skilled in the art, such as distillation, crystallization or chromatography techniques.

[0104] Certain compounds described herein contain one or more asymmetric centers and are capable of existing in various stereoisomeric forms. The present invention contemplates all such possible stereoisomers as well as their racemic and resolved, enantiomerically pure forms and pharmaceutically acceptable salts thereof.

[0105] In addition, when the compounds of this invention form hydrates or solvates they are also within the scope of this invention.

[0106] The compounds of the formula I which are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate a compound of the formula I from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent, and subsequently convert the free base to a pharmaceutically acceptable acid addition salt.

[0107] The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent such as methanol or ethanol. Upon car ful vaporation of th solvent, the d sired solid salt is obtained.

[0107] The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the basic compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

[0108] Those compounds of the formula I which are also acidic in nature, e.g., where R³ includes a COOH or tetrazole moiety, are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the herein described acidic compounds of formula I. These non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium, calcium and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum product yields.

[0109] Also included within the scope of this invention are bioprecursors (also called prodrugs) of the compounds of the formula I. A bioprecursor of a compound of the formula I is a chemical derivative thereof which is readily converted back into the parent compound of the formula I in biological systems. In particular, a bioprecursor of a compound of the formula I is converted back to the parent compound of the formula I after the bioprecursor has been administered to, and absorbed by, a mammalian subject, e.g., a human subject.

[0110] The subject invention also includes isotopically-labelled compounds, which are identical to those recited in formula I, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ²H, ³H, ¹³C, ¹⁴C, ¹⁵N, ¹⁸O, ¹⁷O, ³¹P, ³²P, ³⁵S, ¹⁸F, and ³⁶Cl, respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ³H and ¹⁴C are incorporated, are useful in drug and/or substrate tissue distribution assay. Tritiated, i.e., ³H, and carbon-14, i.e., ¹⁴C, isotopes are particularly preferred for their ease of presentation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ²H, can afford therapeutic advantage resulting from greater metabolic stability, for example increased *In vivo* half-life or reduced dosage requirement and, hence, may be preferred in some circumstances. Isotopically labelled compounds of formula I of this invention and prodrugs thereof can generally be prepared by carrying out the procedure disclosed in above-disclosed Schemes and/or Examples and Preparations below, by submitting a readily available isotopically labelled reagent for a non-isotopically labeled reagent.

[0111] The compounds of the formula I of this invention can be administered via either the oral, parenteral or topical routes to mammals. In general, these compounds are most desirably administered to humans in doses ranging from 0.01 mg to 100 mg per kg of body weight per day, although variations will necessarily occur depending upon the weight, sex and condition of the subject being treated, the disease state being treated and the particular route of administration chosen. However, a dosage level that is in the range of from 0.1 mg to 10 mg per kg of body weight per day, single or divided dosage is most desirably employed in humans for the treatment of abovementioned diseases.

[0112] These compounds are most desirably administered to said non-human mammals, e.g. dogs, cats, horses or livestock in an amount, expressed as mg per kg of body weight of said member per day, ranging from about 0.01 mg/kg to about 20.0 mg/kg/day, preferably from about 0.1 mg/kg to about 12.0 mg/kg/day, more preferably from about 0.5 mg/kg to about 10.0 mg/kg/day, and most preferably from about 0.5 mg/kg to about 8.0 mg/kg/day.

[0113] The compounds of the present invention may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by either of the above routes previously indicated, and such administration can be carried out in single or multiple doses. More particularly, the novel therapeutic agents of the invention can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, trochees, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various nontoxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the therapeutically active compounds of this invention are present in such dosage forms at concentration levels ranging 5% to 70% by weight, preferably 10% to 50% by weight.

[0114] For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dipotassium phosphate and glycine may be employed along with various disintegrants such as starch and preferably corn, potato or tapioca starch, alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatine capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various combinations thereof.

[0115] For parenteral administration, solutions of a compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered (preferably pH>8) if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intra-articular, intra-muscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art. Additionally, it is also possible to administer the compounds of the present invention topically when treating inflammatory conditions of the skin and this may preferably be done by way of creams, jellies, gels, pastes, ointments and the like, in accordance with standard pharmaceutical practice.

[0116] The compounds of formula I may also be administered in the form of suppositories for rectal or vaginal administration of the active ingredient. These compositions can be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at room temperature (for example, 10°C to 32°C) but liquid at the rectal temperature and will melt in the rectum or vagina to release the active ingredient. Such materials are polyethylene glycols, cocoa butter, suppository and wax.

[0117] For buccal administration, the composition may take the form of tablets or lozenges formulated in conventional manner.

Combination with Other Drugs:

[0118] Compounds of formula I would be useful for, but not limited to, the treatment of inflammation in a subject, and for treatment of other inflammation-associated disorders, such as, as an analgesic in the treatment of pain and headaches, or as an antipyretic for the treatment of fever. For example, combinations of the invention would be useful to treat arthritis, including but not limited to rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis. Such combinations of the invention would be useful in the treatment of asthma, bronchitis, menstrual cramps, tendinitis, bursitis, and skin related conditions such as psoriasis, eczema, burns and dermatitis. Combinations of the invention also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease. Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis and for the prevention of colorectal cancer. Combinations of the invention would be useful in creating inflammation in such diseases as vascular diseases, migraine headaches, periarthritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, myasthenia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, hypersensitivity, conjunctivitis, swelling occurring after injury, myocardial ischemia, and the like. The combinations would also be useful for the treatment of certain central nervous system disorders such as Alzheimer's disease and dementia. The combinations of the invention are useful as anti-inflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects. These compositions would also be useful in the treatment of allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis and central nervous system damage resulting from stroke, ischemia and trauma.

[0119] Compounds of formula I will be useful as a partial or complete substitute for conventional NSAID's in preparations wherein they are presently co-administered with other agents or ingredients. Thus, the invention encompasses pharmaceutical compositions for treating COX-2 mediated diseases as defined above comprising a non-toxic therapeutically effective amount of the compound of formula I and one or more ingredients such as another pain reliever including acetaminophen or phenacetin; a potentiator including caffeine; an H₂-antagonist, aluminum or magnesium hydroxide, simethicone, a decongestant including phenylephrine, phenylpropanolamine, pseudoephedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levodopa-ephedrine; an antitussive including codeine, hydrocodone, caramiphen, carbetapentane, or dextromethorphan; a prostaglandin including misoprostol, enprostil, rioprostil, omoprostol or rosaprostol; a diuretic; a sedating or non-sedating antihistamine; anticancer agents such as angiotatin and endostatin; anti-Alzheimers such as Donepezil and Tacrin hydrochloride; and TNF alpha inhibitors such as Etanercept.

[0120] These cyclooxygenase inhibitors can further be used in combination with nitric oxide inhibitors disclosed in WO 96/28145.

[0121] Also, the invention encompasses pharmaceutical compositions for treating COX-2 mediated diseases as defined above comprising a non-toxic therapeutically effective amount of the compound of formula I and one or more anti-ulcer agent and/or prostaglandins, which are disclosed in WO 97/11701.

[0122] The useful prostaglandins include misoprostol, plus-minus methyl 11 α , 16-dihydroxy-16-methyl-9-oxoprostaglandin E-en-1-oate; enisoprost and methyl-7-[2B-[6-(1-cyclopenten-1-yl)-4-hydroxy-4-methyl-1E, 5E-hexadienyl]-3 β -hydroxy-5-oxo 1R, 1 α -cydopentyl]-4Z-heptenoate. Prostaglandins within the scope of the invention also include aruprost, enprostil, rioprostol, nocaprost, mexiprostol, ornoprostol, dimoxaprostanide, tiaprostanide and rosaprostanide.

[0123] The present compounds may also be used in co-therapies, partially or completely, in place of other conventional antiinflammatories, such as together with steroids, 5-lipoxygenase inhibitors, LTB₄ antagonists and LTA₄ hydrolase inhibitor's.

[0124] An example of LTB₄ is disclosed in W097/29774. Suitable LTB₄ inhibitors include, among others, ebselen, Bayer Bay-x-1005, Ciba Geigy compound CGS-25019C, Leo Denmark compound ETH-615, Lilly compound LY-293111, Ono compound ONO-4057, Terumo compound TMK-688, Lilly compounds LY-213024, 264086 and 292728, Ono compound ONO-LB457, Searle compound SC-S3228, calcitrol, Lilly compounds LY-210073, LY223982, LY233469, and LY255283, Ono compound ONO-LB-448, Searle compounds SC-41930, SC-50605 and SC-51146, and SK&F compound SKF-104493. Preferably, the LTB4 inhibitors are selected from ebselen, Bayer Bay-x-1005, Ciba Geigy compound CGS-25019C, Leo Denmark compound ETH-615, Lilly compound LY-293111, Ono compound ONO-4057 and Terumo compound TMK-688.

[0125] An example of 5-LO inhibitors is disclosed in W097/29776. Suitable 5-LO inhibitors include, among others, masoprolac, tenidap, zileuton, pranlukast, teponoxalin, rilopirox, flezelastine hydrochloride, enazadrem phosphate and bunaprolast.

[0126] An example of LTA₄ hydrolase inhibitors is disclosed in W097/29774. Suitable LTA₄ hydrolase inhibitors include, among others, Rhone-Poulenc Rorer RP-64966.

[0127] The administration of the present invention may be for either prevention or treatment purposes. The methods and compositions used herein may be used alone or in conjunction with additional therapies known to those skilled in the art in the prevention or treatment of angiogenesis. Alternatively, the methods and compositions described herein may be used as adjunct therapy. By way of example, the cyclooxygenase-2 inhibitor may be administered alone or in conjunction with other antineoplastic agents or other growth inhibiting agents or other drugs or nutrients.

[0128] There are large numbers of antineoplastic agents available in commercial use, in clinical evaluation and in pre-clinical development, which could be selected for treatment of angiogenesis by combination drug chemotherapy. Such antineoplastic agents fall into several major categories, namely, antibiotic-type agents, alkylating agents, antimetabolite agents, hormonal agents, immunological agents, interferon-type agents and a category of miscellaneous agents. Alternatively, other anti-neoplastic agents, such as metallomatrix proteases inhibitors (MMP), such as MMP-13 inhibitors including batistat, marimastat, Agouron Pharmaceuticals AG-3340, and Roche R0-32-3555, or alpha,beta,inhibitors may be used.

[0129] A first family of antineoplastic agents which may be used in combination with a selective cyclooxygenase-2 inhibitor consists of antimetabolite-type antineoplastic agents. Suitable antimetabolite antineoplastic agents may be selected from the group consisting of 5-FU-fibrinogen, acanthifolic acid, aminothiadiazole, brequinar sodium, carmofur, Ciba-Geigy CGP-30694, cyclopentyl cytosine, cytarabine phosphate stearate, cytarabine conjugates, Lilly DATHF, Merrel Dow DDFC, dezaguanine, dideoxycytidine, dideoxyguanosine, didox, Yoshitomi DMDC, doxifluridine, Wellcome EHNA, Merck & Co. EX-015, fazarabine, flouxuridine, fludarabine phosphate, 5-fluorouracil, N-(2'-furanidyl)-5-fluorouracil, Daiichi Seiyaku F0-152, isopropyl pyrrolizine, Lilly LY-188011, Lilly LY-264618, methobenzaprim, methotrexate, Wellcome MZPES, norspermidine, NCI NSC-127716, NCI NSC-264880, NCI NSC-39661, NCI NSC-612567, Warner-Lambert PALA, pentostatin, piritrexim, plicamycin, Asahi Chemical PL-AC, Takeda TAC-788, thioguanine, tiazofurin, Erbamont TIF, trimetrexate, tyrosine kinase Inhibitors, tyrosine protein kinase Inhibitors, Taiho UFT and uracytin.

[0130] A second family of antineoplastic agents which may be used in combination with a selective cyclooxygenase-2 inhibitor consists of alkylating-type antineoplastic agents. Suitable alkylating-type antineoplastic agents may be selected from the group consisting of Shionogi 254-S, aldo-phosphamide analogues, altretamine, anaxirone, Boehringer Mannheim BBR-2207, bestabucil, budotitane, Wakunaga CA-102, carboplatin, carmustine, Chinoim-139, Chinoim-153, chlorambucil, cisplatin, cyclophosphamide, American Cyanamid CL-286558, Sanofi CY-233, cyplatate, Degussa D-19-384, Sumimoto DACHP(Myr)2, diphenylspiromustine, diplatinum cytostatic, Erba distamycin derivatives, Chugai DWA-2114R, ITI E09, elmustine, Erbamont FCE-24517, estramustine phosphate sodium, fotemustine, Unimed G-6-M, Chinoim GYKI-17230, hepsul-fam, ifosfamide, iproplatin, lomustine, mafosfamide, mitolactol, Nippon Kayaku NK-121, NCI NSC-264395, NCI NSC-342215, oxaliplatin, Upjohn PCNU, prednimustine, Proter PTT-II9, ranimustine, semusline, SmithKline SK&F-101772, Yakult Honsha SN-22, spiromus-line, Tanabe Selyaku TA-077, tauromustine, temozolamide, teroxirone, tetraplatin and trimelamol.

[0131] A third family of antineoplastic agents which may be used in combination with a selective cyclooxygenase-2 inhibitor consists of antibiotic-type antineoplastic agents. Suitable antibiotic-type antineoplastic agents may be selected

from the group consisting of Taiho 4181-A, aclarubicin, actinomycin D, actinoplanon , Erbamont ADR-456, aeroplysinin derivative, Ajinomoto AN-201-II, Ajinomoto AN-3, Nippon Soda anisomycins, anthracycline, azino-mycin-A, bisucaberin, Bristol-Myers BL-6859, Bristol-Myers BMY-25067, Bristol-Myers BMY-25551, Bristol-Myers BMY-26605, Bristol-Myers BMY-27557, Bristol-Myers BMY-28438, bleomycin sulfate, bryostatin-1, Taiho C-1027, calichemycin, chromoximycin, dactinomycin, daunorubicin, Kyowa Hakko DC-102, Kyowa Hakko DC-79, Kyowa Hakko DC-8BA, Kyowa Hakko DC89-AI, Kyowa Hakko DC92-B, ditrisarubicin B, Shionogi DOB-41, doxorubicin, doxorubicin-fibrinogen, elsamycin-A, epirubicin, erstatin, esorubicin, esperamicin-A1, esperamicin-Alb, Erbamont FCE-21954, Fujisawa FK-973, foscarnet, Fujisawa FR-900482, glidobactin, gregatin-A, grincamycin, herbimycin, idarubicin, illudins, kazusamycin, kesarirhodins, Kyowa Hakko KM-5539, Kirin Brewery KRN-8602, Kyowa Hakko KT-5432, Kyowa Hakko KT-5594, Kyowa Hakko KT-6149, American Cyanamid LL-D49194, Meiji Seika ME 2303, menogaril, mitomycin, mitoxantrone, Smith-Kline M-TAG, neoenactin, Nippon Kayaku NK-313, Nippon Kayaku NKT-OI, SRI International NSC-357704, oxalysine, oxaunomycin, peplomycin, pilatin, pirarubicin, porothramycin, pyrindamycin A, Tobishi RA-I, rapamycin, rhizoxin, roedorubicin, sibanomicin, silvenmycin, Sumitomo SM-5887, Show Brand SN-706, Show Brand SN-07, sorangicin-A, sparsomycin, SS Pharmaceutical SS-21020, SS Pharmaceutical SS-7313B, SS Pharmaceutical SS-9816B, steffimycin B, Taiho 4181-2, talisomycin, Takeda TAN-868A, terpentine, thiazine, tricrozarin A, Upjohn U-73975, Kyowa Hakko UCN-10028A, Fujisawa WF-3405, Yoshitomi Y-2S024 and zorubicin.

[0132] A fourth family of antineoplastic agents which may be used in combination with the selective cyclooxygenase-2 inhibitor consists of a miscellaneous family of antineoplastic agents selected from the group consisting of alpha-carotene, alpha-difluoromethyl-arginine, acitretin, Biotec AD-5, Kyorin AHC-52, alstonine, amoneafide, amphethinile, amsacrine, Angiostat, ankinomycin, anti-neoplaston AIO, antineoplaston A2, antineoplaston A3, antineoplaston A5, antineoplaston AS2-1, Henkel APD, aphidicolin glycinate, asparaginase, Avarol, baccharin, batracylin, benfluron, benzotript, Ipsen-Beaufour BIM-23015, bisantrene, Bristol-Myers BMY-40481, Vestar boron-IO, bromofosfamide, Wellcome BW-502, Wellcome BW-773, caracemide, carmethylazole hydrochloride, Ajinomoto CDAF, chlorsulfiquinoxalone, Chemes CHX-2053, Chemex CHX-100, Warner-Lambert CI-921, Warner-Lambert CI-937, Warner-Lambert CI-941, Warner-Lambert CI-958, clafenur, claviridenone, ICN compound 1259, ICN compound 4711, Contracan, Yakult Honsha CPT-11, crisnatol, curaderm, cytochalasin B, cytarabine, cytocytin, Merz D-609, DABIS maleate, dacarbazine, datelliptinium, didemnin-B, dihaematoporphyrin ether, dihydrolenperone, dinanine, distamycin, Toyo Pharmar DM-341, Toyo Pharmar DM-75, Daiichi Seiyaku DN-9693, elliprinabin, elliptinium acetate, Tsumura EPMTc, ergotamine, etoposide, etretinate, fenretinide, Fujisawa FR-57704, gallium nitrate, genkwadaphnin, Chugai GLA-43, Glaxo GR-63178, grifolan NMF-5N, hexadecylphosphocholine, Green Cross H0-221, homoharringtonine, hydroxyurea, BTG ICRF-187, ilmofosine, isoglutamine, isotretinoin, Otsuka JI-36, Ramot K-477, Otsuak K-76COONA, Kureha Chemical K-AM, MECT Corp KI-8110, American Cyanamid L-623, leukoregulin, Ionidamine, Lundbeck LU-23-112, Lilly LY-186641, NCI (US) MAP, marycin, Merrel Dow MDL-27048, Medco MEDR-340, merbarone, merocyanine derivatives, methyl-anilinoacridine, Molecular Genetics MGI-136, minactivin, mitonafide, mitoquidone, mepidamol, motretinide, Zenyaku Kogyo MST-16, N-(retinoyl)amino acids, Nisshin Flour Milling N-021, N-acylated-dehydroalanines, nafazatrom, Talso NCU-190, nocodazole derivative, Normosang, NCI NSC-145813, NCI NSC-361456, NCI NSC-604782, NCI NSC-95580, octreotide, Ono ONO-112, oquizanocene, Akzo Org-10172, pancratistatin, pazelliptine, Warner-Lambert PD-111707, Warner-Lambert PD-115934, Warner-Lambert PD-131141, Pierre Fabre PE-IOOI, ICRT peptide D, piroxantine, polyhaematoporphyrin, polypreic acid, Efamol porphyrin, probimane, procarbazine, proglurnide, Invitron protease nexin I, Tobishl RA-700, razoxane, Sapporo Breweries RBS, restrictin-P, retelliptine, retinolc acid, Rhone-Poulenc RP-49532, Rhone-Poulenc RP-56976, SmithKline SK&F-104864, Sumitomo SM-108, Kuraray SMANCS, SeaPharm SP-10094, spatol, spirocyclopropane derivatives, spirogermanium, Unimed, SS Pharmaceutical SS-554, strypoldinone, Stypoldione, Suntory SUN 0237, Suntory SUN 2071, superoxide dismutase, Toyama T-506, Toyama T-680, taxol, Teijin TEI-0303, teniposide, thaliblastine, Eastman Kodak TJB-29, tocotrienol, Topostin, Teijin TT-82, kyowa Hakko UCN-OI, Kyowa Hakko UCN-1028, ukrain, Eastman Kodak USB-006, vinblastine sulfate, vincristine, vindesine, vinestramide, vinorelbine, vintripotol, vinzolidine, withanolides and Yamanouchi YM-534.

[0133] Examples of radioprotective agents which may be used in the combination chemotherapy of this invention are AD-5, adchnon, amifostine analogues, detox, dimesna, I-102, MN-159, N-acylated-dehydroalanines, TGF-Genentech, tiprotimod, amifostine, WR-151327, FUT-187, ketoprofen transdermal, naburnetone, superoxide dismutase (Chiron) and superoxide disrtutase Enzon.

[0134] Methods for preparation of the antineoplastic agents described above may be found in the literature. Methods for preparation of doxorubicin, for example, are described in U.S. Patents No. 3,590,028 and No. 4,012,448. Methods for preparing metallomatrix protease inhibitors are described in EP 780386, W097/20824, W096/15096. Methods for preparing SOD mimics are described in EP 524,101. Methods for preparing alpha,beta, inhibitors are described in W097/08174.

[0135] In addition, the selective COX-2 inhibitor may be administered in conjunction with other antiinflammatory agents for maximum safety and efficacy, including NSAID's, selective COX-1 inhibitors and inhibitors of the leukotriene pathway, including 5-lipoxygenase inhibitors. Examples of NSAID's include indomethacin, naproxen, ibuprofen, sali-

cyclic acid derivatives such as aspirin, diclofenac, ketorolac, piroxicam, meloxicam, mefenamic acid, sulindac, tilmelitin sodium, zomepirac, fenoprofen, phenylbutazone, oxyphenbutazone, nimesulid, zaltoprofen and letodolac.

Methods of Assessing Biological Activities:

[0136] Activities of the compounds of the formula I of the present invention may be demonstrated by the following assays.

In vitro assays:

Human cell based COX-1 assay:

[0137] Human peripheral blood obtained from health volunteers is diluted to 1/10 volume with 3.8% sodium citrate solution. The platelet-rich plasma immediately obtained is washed with 0.14M sodium chloride solution containing 12mM Tris-HCl (pH 7.4) and 1.2mM EDTA. Platelets are then washed with platelet buffer (Hanks buffer (calcium free) containing 0.2% BSA and 20mM Hepes buffer). Finally, the human washed platelets (HWP) are suspended in platelet buffer at the concentration of 2.85×10^8 cells/ml and stored at room temperature until used. The HWP suspension (70 μ l aliquots, final 2.0×10^7 cells/ml) is placed in a 96-well U bottom plate and 10 μ l aliquots of 12.6mM CaCl₂ is added. Platelets are incubated with A23187 (final 10 μ M, Sigma) with a test compound (0.1 - 100 μ M) dissolved in DMSO (final concentration; less than 0.01%) at 37°C for 15 minutes. The reaction is quenched by adding EDTA (final 7.7mM), and TXB₂ in the supernatant quantitated by using a radioimmunoassay kit (supplied by Amersham) according to the manufacturer's procedure.

Human Cell Based COX-2 Assay:

[0138] The human cell based COX-2 assay is carried as previously reported by Moore *et al.*, *Inflamm. Res.*, Vol. 45, pp. 54- , 1996. Confluent human umbilical vein endothelial cells (HUVECs, Morinaga) in a 96-well U bottom plate are washed with 100 μ l of RPMI1640 containing 2% FCS and incubation with hIL-1 α (final concentration 300U/ml, R & D Systems) at 37°C for 24 hours. After washing, the activated HUVECs are stimulated with A23187 (final concentration 30 μ M) in Hanks buffer containing 0.2% BSA, 20mM Hepes and a test compound (0.1nM - 100 μ M) dissolved in DMSO (final concentration; less than 0.01%) 37°C for 15 minutes. 6-Keto-PGF_{1 α} , stable metabolite of PG_{I₂}, in the supernatant is quantitated after adequate dilution by using a radioimmunoassay kit (supplied by Amersham) according to the manufacturer's procedures.

Canine In vitro assays

[0139] The following canine cell based COX 1 and COX-2 assays have been reported in Ricketts *et al.*, Evaluation of Selective Inhibition of Canine Cyclooxygenase 1 and 2 by Carprofen and Other Nonsteroidal Anti-inflammatory Drugs, American Journal of Veterinary Research, 59(11), 1441-1446.

Protocol for Evaluation of Canine COX-1 Activity

[0140] Test drug compounds were solubilized and diluted the day before the assay was to be conducted with 0.1 mL of DMSO / 9.9 mL of Hank's balanced salts solution (HBSS), and stored overnight at 4° C. On the day that the assay was carried out, citrated blood was drawn from a donor dog, centrifuged at 190 x g for 25 minutes at room temperature, and the resulting platelet-rich plasma was then transferred to a new tube for further procedures. The platelets were washed by centrifuging at 1500 x g for 10 minutes at room temperature. The platelets were washed with platelet buffer comprising Hank's buffer (Ca free) with 0.2% bovine serum albumin (BSA) and 20 mM HEPES. The platelet samples were then adjusted to 1.5×10^7 / mL, after which 50 μ l of calcium ionophore (A23187) together with a calcium chloride solution were added to 50 μ l of test drug compound dilution in plates to produce final concentrations of 1.7 μ M A23187 and 1.26 mM Ca. Then, 100 μ l of canine washed platelets were added and the samples were incubated at 37°C for 15 minutes, after which the reaction was stopped by adding 20 μ l of 77 mM EDTA. The plates were then centrifuged at 2000 x g for 10 minutes at 4°C, after which 50 μ l of supernatant was assayed for thromboxane B₂ (TXB₂) by enzyme-immunoassay (EIA). The pg/mL of TXB₂ was calculated from the standard line included on each plate, from which it was possible to calculate the percent inhibition of COX-1 and the IC₅₀ values for the test drug compounds.

Protocol for Evaluation of Canine COX-2 Activity

[0141] A canine histiocytoma (macrophage-like) cell line from the American Type Culture Collection designated as DH82, was used in setting up the protocol for evaluating the COX-2 inhibition activity of various test drug compounds. There was added to flasks of these cells 10 pg/mL of LPS, after which the flask cultures were incubated overnight. The same test drug compound dilutions as described above for the COX-1 protocol were used for the COX-2 assay and were prepared the day before the assay was carried out. The cells were harvested from the culture flasks by scraping, and were then washed with minimal Eagle's media (MEM) combined with 1% fetal bovine serum, centrifuged at 1500 rpm for 2 minutes, and adjusted to a concentration of 3.2×10^5 cells/mL. To 50 µL of test drug dilution there was added 50 µL of arachidonic acid in MEM to give a 10 pM final concentration, and there was added as well 100 µL of cell suspension to give a final concentration of 1.6×10^5 cells/mL. The test sample suspensions were incubated for 1 hr and then centrifuged at 1000 rpm for 10 minutes at 4°C, after which 50 µL aliquots of each test drug sample were delivered to EIA plates. The EIA was performed for prostaglandin E₂ (PGE₂), and the pg/mL concentration of PGE₂ was calculated from the standard line included on each plate. From this data it was possible to calculate the percent inhibition of COX-2 and the IC₅₀ values for the test drug compounds. Repeated investigations of COX-1 and COX-2 inhibition were conducted over the course of several months. The results are averaged, and a single COX-1 : COX-2 ratio is calculated.

[0142] Whole blood assays for COX-1 and COX-2 are known in the art such as the methods described in C. Brideau, et al., A Human Whole Blood Assay for Clinical Evaluation of Biochemical Efficacy of Cyclooxygenase Inhibitors, Inflammation Research, 45, 68-74, (1996). These methods may be applied with feline, canine or human blood as needed.

In vivo Assays:

Canine whole blood ex vivo determinations of COX-1 and COX-2 activity inhibition

[0143] The *in vivo* inhibitory potency of a test compound against COX-1 and COX-2 activity may be evaluated using an *ex vivo* procedure on canine whole blood. Three dogs were dosed with 5 mg/kg of the test compound administered by oral gavage in 0.5% methylcellulose vehicle and three dogs were untreated. A zero-hour blood sample was collected from all dogs in the study prior to dosing, followed by 2- and 8-hour post-dose blood sample collections. Test tubes were prepared containing 2µL of either (A) calcium ionophore A23187 giving a 50 µM final concentration, which stimulates the production of thromboxane B₂ (TXB₂) for COX-1 activity determination; or of (B) lipopolysaccharide (LPS) to give a 10 pg/mL final concentration, which stimulates the production of prostaglandin E₂ (PGE₂) for COX-2 activity determination. Test tubes with unstimulated vehicle were used as controls. A 500 µL sample of blood was added to each of the above-described test tubes, after which they were incubated at 37°C for one hr in the case of the calcium ionophore-containing test tubes, and overnight in the case of the LPS-containing test tubes. After incubation, 10 µL of EDTA was added to give a final concentration of 0.3%, in order to prevent coagulation of the plasma which sometimes occurs after thawing frozen plasma samples. The incubated samples were centrifuged at 4°C and the resulting plasma sample of ~200 µL was collected and stored at -20°C in polypropylene 96-well plates. In order to determine endpoints for this study, enzyme immunoassay (EIA) kits available from Cayman were used to measure production of TXB₂ and PGE₂, utilizing the principle of competitive binding of tracer to antibody and endpoint determination by colorimetry. Plasma samples were diluted to approximate the range of standard amounts which would be supplied in a diagnostic or research tools kit, i.e., 1/500 for TXB₂ and 1/750 for PGE₂.

[0144] The data set out in Table 2 below show how the percent inhibition of COX-1 and COX-2 activity is calculated based on their zero hour values. The data is expressed as treatment group averages in pg/ml of TXB₂ and PGE₂ produced per sample. Plasma dilution was not factored in said data values.

[0145] The data in Table 2 show that, in this illustration, at the 5 mg/kg dose there was significant COX-2 inhibition at both timepoints. The data in Table 2 also show that at the 5 mg/kg dose there was no significant inhibition of COX-1 activity at the timepoints involved. Accordingly, the data in Table 2 clearly demonstrates that at the 5 mg/kg dosage concentration this compound possesses good COX-2 selectivity.

TABLE 2

COX-1 ACTIVITY INHIBITION - Group Averages					
	TXB ₂ Pg/Ml/Well			Percent Inhibition	
Hour	0-hour	2-hour	8-hour	2-hour	8-hour
Untreated	46	45	140	2%	0%
5 mg/kg	41	38	104	7%	0%

TABLE 2 (continued)

COX-2 ACTIVITY INHIBITION - Group Averages						
	PGE ₂ Pg/mL/Well			Percent Inhibition		
Hour	0-hour	2-hour	8-hour	2-hour	8-hour	
Untreated	420	486	501	0%	0%	
5 mg/kg	711	165	350	77%	51%	

- [0146] COX inhibition is observed when the measured percent inhibition is greater than that measured for untreated controls. The percent inhibition in the above table is calculated in a straightforward manner in accordance with the following equation:

$$\% \text{ Inhibition (2-hour)} = \frac{(PGE_2 \text{ at } t = 0) - (PGE_2 \text{ at } t = 2)}{(PGE_2 \text{ at } t = 0)}$$

Carageenan induced foot edema in rats

- [0147] Male Sprague-Dawley rats (5 weeks old, Charles River Japan) are fasted overnight. A line is drawn using a marker above the ankle on the right hind paw and the paw volume (V0) is measured by water displacement using a plethysmometer (Murromachi). Animals are given orally either vehicle (0.1% methyl cellulose or 5% Tween 80) or a test compound (2.5ml per 100g body weight). One hour later, the animals are then injected intradermally with \square -carageenan (0.1ml of 1% w/v suspension in saline, Zushikagaku) into right hind paw (Winter *et al.*, *Proc. Soc. Exp. Biol. Med.*, Vol. 111, p. 544-, 1962; Lombardino *et al.*, *Arzneim. Forsch.*, Vol. 25, p. 1629-, 1975) and three hours later, the paw volume (V3) is measured and the increase in volume (V3-V0) calculated. Since maximum inhibition attainable with classical NSAIDs is 60 - 70%, ED₅₀ values are calculated.

Gastric ulceration in rats

- [0148] The gastric ulcerogenicity of a test compound is assessed by a modification of the conventional method (Ezer *et al.*, *J. Pharm. Pharmacol.*, Vol. 28, p. 655-, 1976; Cashin *et al.*, *J. Pharm. Pharmacol.*, Vol. 29, pp. 330-336, 1977). Male Sprague-Dawley rats (5 weeks old, Chales River Japan), fasted overnight, were given orally either vehicle (0.1% m thyl cellulose or 5% Tween 80) or a test compound (1ml per 100g body weight). Six hours after, the animals are sacrificed by cervical dislocation. The stomachs are removed, inflated with 1% formalin solution (10ml), opened by cutting along the grater curvature. From the number of rats that show at least gastric ulcer or haemorrhaging erosion (including ecchymosis), the incidence ulceration is calculated. Animals do not have access to either food or water during the experiment.

Data Analysis:

- [0149] Statistical program packages, SYSTANT (SYSTANT, INC.) and StatView (Abacus Concepts, Inc.) for Macintosh are used. Difference between test compound treated groups and control group are tested for using ANOVA. The IC₅₀ (ED₅₀) values are calculated from the equation for the log-linear regression of concentration (dose) versus percent inhibition.

[0150] Most compounds prepared in the Working Examples as described hereinafter were tested by at least one of the methods described above, and showed IC₅₀ values of 0.001 μ M to 3 μ M with respect to inhibition of COX-2 in either the canine or human assays.

[0151] The following examples contain detailed descriptions of the methods of the preparation of compounds of formula I. These detailed descriptions fall within the scope of the invention and serve to exemplify the above described general synthetic procedures which form part of the invention. These detailed descriptions are presented for illustrative purposes only and are not intended to restrict the scope of the present invention.

Examples and Preparations

- [0152] The invention is illustrated in the following non-limiting examples in which, unless stated otherwise: all operations w r carried out at room or ambient temp rature, that is, in th range of 18-25 °C; evaporation of solvent was carried out using a rotary evaporator under reduced pressure with a bath of up to 60 °C; reactions were monitored by

thin layer chromatography (tlc) and reaction times are given for illustration only; melting points (m.p.) given are uncorrected (polymorphism may result in different melting points); structure and purity of all isolated compounds were assured by at least one of the following techniques: tlc (Merck silica gel 60 F-254 precoated plates), mass spectrometry, nuclear magnetic resonance (NMR) or infrared spectroscopy (IR). IR data were obtained on a FTIR 8200 (SHIMAZU Spectrometer). Yields are given for illustrative purposes only. Flash column chromatography was carried out using Merck silica gel 60 (230–400 mesh ASTM). Low-resolution mass spectral data (EI) were obtained on a Automass 120 (JEOL) mass spectrometer. Liquid Chromatography data was collected on a Hewlett Packard 1100 Liquid Chromatography/Mass Selective Detector (LC/MSD). Analysis was performed on a Luna C-18 column with dimensions of 3.0x150 mm. The flow rate was 0.425 ml/min running a gradient of 50% 0.1% aqueous formic acid and 50% acetonitrile to 100% acetonitrile in 15 minutes. The ionization type for the mass detector of the Mass Spectrophotometer was atmospheric pressure electrospray in the positive ion mode with a fragmentor voltage of 50 volts. NMR data was determined at 270 MHz (JEOL JNM-LA 270 spectrometer) using deuterated chloroform (99.8% D), methanol (99.8% D) or dimethylsulfoxide (99.9% D) as solvent unless indicated otherwise, relative to tetramethylsilane (TMS) as internal standard in parts per million (ppm); conventional abbreviations used are: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, etc.

[0153] The following abbreviations are used:

THF:	tetrahydrofuran
CH ₂ Cl ₂ :	dichloromethane
NaHCO ₃ :	sodium bicarbonate
HCl:	hydrogen chloride
MgSO ₄ :	magnesium sulfate
Na ₂ SO ₄ :	sodium sulfate
DME:	dimethoxyethane
n-BuLi:	n-butyllithium
DMF:	dimethylformamide

EXAMPLE 1

[0154] 5-[4-(2-Furyl)phenyl]-1-[2-(methylsulfonylpyridin)-5-yl]-3-trifluoromethyl-1H-pyrazole 4,4,4-Trifluoro-1-[4-(2-furyl)phenyl]butane-1,3-dione. (step 1)

To a stirred solution of 4,4,4-trifluoro-1-(4-bromophenyl)butane-1,3-dione (1 g, 3.39 mmol, *J. Med. Chem.*, 1997, 40, 1347) in DME (40 mL) was added furan-2-boronic acid (0.455 g, 4.07 mmol), bis(triphenylphosphine) palladium(\square)chloride (0.271 g, 0.386 mmol) and saturated NaHCO₃ solution (12 mL) at room temperature under nitrogen. The mixture was heated at reflux temperature for 5 hours, and cooled down to room temperature. The reaction mixture was filtered through celite, the filtrate was poured into water and the whole was extracted with ethyl acetate (30 mL x 3). The organic layer was washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by flash chromatography eluting with hexane / ethyl acetate (3 / 1) to give the subtitle compound (0.586 g, 61.2 % yield).

MS (EI): m/z 282 (M⁺)

¹H-NMR (DMSO-d₆) δ: 7.95 (2H, d, J=8.1 Hz), 7.78 (2H, d, J=8.1 Hz), 7.81 (1H, s), 7.10 (1H, s), 6.64 (1H, s), 6.31 (1H, s)

[0155] 5-[4-(2-Furyl)phenyl]-1-[2-(methylsulfonylpyridin)-5-yl]-3-trifluoromethyl-1H-pyrazole. (step 2)

5-Hydrazino-2-(methylsulfonyl)pyridine hydrochloride (0.250 g, 0.89 mmol) was added to a solution of 4,4,4-Trifluoro-1-[4-(2-furyl)phenyl]butane-1,3-dione from step 1 (0.22 g, 0.97 mmol) in EtOH (11 mL). The mixture was heated at reflux temperature for 17 hours and cooled down to room temperature. The reaction mixture was concentrated *in vacuo*, and the residue was taken up in ethyl acetate, washed with water and brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by flash chromatography eluting with hexane / ethyl acetate (3/1). The resulting solid was recrystallized from ethyl acetate / hexane to give the title compound (0.15 g, 42 % yield). mp: 106–109°C

¹H-NMR (CDCl₃) δ: 8.74 (d, J = 2.3 Hz, 1H), 8.98 (d, J = 8.4 Hz, 1H), 7.94 (dd, J = 2.5, 8.6 Hz, 1 H), 7.72 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 1.5 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H), 6.84 (s, 1 H), 6.75 (d, J = 3.3 Hz, 1 H), 6.52 (dd, J = 1.6, 3.3 Hz, 1H), 3.24 (s, 3H).

Anal. Calcd. for C₂₀H₁₄N₃O₃F₃S: C, 55.43; H, 3.26; N, 9.70. Found: C, 55.55; H, 3.36; N, 9.79.

Preparation 15-Hydrazino-2-(methylsulfonyl)pyridine hydrochloride

- 5 [0156] To a solution of 3-amino-6-(methylsulfonyl)pyridine (3.0 g, 0.017 mol, F. Walker et al., *J. Chem. Soc.* 1939 (1948)) in conc HCl (23 mL), sodium nitrite (1.4 g, 0.019 mmol) in H₂O (23 mL) was added dropwise at 0°C and the mixture was stirred for 40 minutes at 0°C. Tin (II) chloride dihydrate (19 g, 0.085 mol) in conc HCl (25 mL) was added dropwise at 0°C. The mixture was stirred for 1 hour at 0°C then for 1 hour at room temperature. The mixture was basified with aqueous NaOH (pH=12) with ice cooling and THF (200 mL) was added and stirred for 30 minutes. The mixture was filtered by celite and the filtrate was extracted with ethyl acetate (50 mL x 2), washed with H₂O (100 mL) and brine (100 mL), dried (MgSO₄) and concentrated *in vacuo* gave 0.65 g of brown solid. The solid was terated with 10 % methanolic HCl (50 mL), and volatiles were removed by evaporation. The residue was washed with ethanol and dichloromethane to give the title compound (0.45 g, 12%).

15 ¹H-NMR (DMSO-d₆) δ: 8.40-8.37 (m, 1H), 7.96 (d, J = 8.6 Hz, 1H), 7.55-7.45 (m, 1H), 3.19 (s, 3H).

Preparation of 3-pyridyl hydrazinePreparation of 3-nitro-6-(methylthio)pyridine from 2-mercaptop-5-nitropyridine.

- 20 [0157] 2-Mercapto-5-nitro pyridine (20.0 g, 128 mmol) was suspended in H₂O/ethanol (43 mL/13 mL). Sodium carbonate monohydrate (17.49 g, 141 mmol, dissolved in 86 mL of H₂O) was added to the above slurry dropwise. Methyl iodide (20.0 g, 141 mmol) was added to the above mixture and the mixture was stirred at rt for 1 h. The solid was filtered and washed with water and ethanol to provide the title compound in quantitative yield.

Preparation of 3-nitro-6-(methylsulfonyl)pyridine from 3-nitro-6-(methylthio)pyridine.

- 25 [0158] 3-Nitro-6-(methylthio)pyridine (22.0 g, 129.3 mmol) was dissolved in acetone (140 mL). Sulfuric acid (2N, 230 mL) was then added dropwise to above solution to form a slurry. KMnO₄ (26.5 g, 168.1 mmol, dissolved in 500 mL of H₂O) was added to the above mixture dropwise. The mixture that resulted was stirred at rt overnight. The solid was filtered and stirred with a warm mixture of ethanol/methanol (10/1). The insoluble salt was filtered, the filtrate was concentrated to provide a pale yellow solid. The crude product was recrystallized from ethanol to furnish the title compound (17.8 g, 70%).

Preparation of 3-amino-6-(methylsulfonyl)pyridine from 3-nitro-6-(methylsulfonyl)pyridine

- 35 [0159] 3-Nitro-6-(methylsulfonyl)pyridine (10 g, 49.5 mmol) was suspended in water (200 mL). Iron powder (5.0 g, 89.3 mmol) and acetic acid (0.5 mL) were added to the above mixture. The mixture, which resulted, was heated to reflux for 2h. The reaction was monitored by TLC (EtOAc/hexane, 1/1). The reaction mixture was then cooled to rt and a saturated solution of NaHCO₃ (100 mL) was added to the mixture. Ethyl acetate (200 mL) was added to the above mixture and the mixture which resulted was stirred at rt for 30 minutes. The mixture was filtered through celite and the organic layer was collectd. The aqueous layer was extracted with ethyl acetate (200 mL x 3). The organic extractions were combined and dried (Na₂SO₄). The solvent was removed under reduced pressure to provide the 3-amino-6-(methylsulfonyl)pyridine (6g, 70.5%).

Preparation of 5-hydrazino-2-(methylsulfonyl)pyridine from 3-amino-6-(methylsulfonyl)pyridine.

- 45 [0160] To a solution of 3-amino-6-(methylsulfonyl)pyridine (3.72 g, 21.6 mmol) in conc. HCl (30 mL), sodium nitrite (1.78 g, 25.7 mmol) in water (20 mL) was added dropwise at -10 to -15 °C and the mixture was stirred for 2h at -10 to -5 °C (note: check the reaction by TLC to make sure all the starting material was consumed). Tin(II) chloride dihydrate (20 g, 88.6 mmol) in conc. HCl (30 mL) was added dropwise at -5°C. The mixture was stirred 1h at -5°C and then left overnight. The mixture was basified with aqueous NaOH (pH=9) with ice cooling and THF (200 mL) was added and stirred for 30 minutes. The mixture was filtered by celite and the filtrate was extracted with THF (200 mL x 3). The organic extraction was combined and dried (MgSO₄) and concentrated under reduced pressure to provide the title compound (3.2g, 78.8%).

- 55 [0161] 5-hydrazino-2-(methylsulfonyl)pyridine was dissolved in HCl-methanol (10%, 30 mL) and volatiles were removed under reduced pressure. The residue was washed with ether and employed directly to next step without further purification.

Preparation of dlk tones:2-Methoxycarbonyl-4-acetylphenyltrifluoromethanesulfonate

- 5 [0162] Methyl-5-acetylsalicylate (5.02g, 25.8mmol) was dissolved in dry methylene chloride (130ml) and chilled to -30°C. 2,6-Lutidine (3.32g, 31mmol) and N,N-dimethylaminopyridine (630mg, 5.17mmol) were added. Trifluoromethanesulfonic anhydride (8.75g, 31mmol) was added in portions over 1 minute. The reaction was allowed to warm slowly to room temperature over two hours, and then stirred an additional hour at room temperature. The solution was washed with water and brine, dried over sodium sulfate, filtered, and evaporated to give the title compound, which was used without further purification.

4-(2-furyl)-3-(methoxycarbonyl)phenyl-1-ethanone

- 15 [0163] Crude 2-Methoxycarbonyl-4-acetylphenyltrifluoromethanesulfonate (25.8mmol) was dissolved in dioxane (250ml). 2-Tributylstannylfuran (10.28g, 28.8mmol), tetrakis(triphenylphosphine)palladium (2.77g, 2.4mmol) and lithium chloride (2.54g, 60mmol) were added, and the mixture heated to reflux under nitrogen 8 hours. The mixture was cooled and the solvent was removed under reduced pressure. The residue was taken up in ethyl acetate and filtered through glass microfiber filter paper to remove precipitated palladium(0). The filtrate was extracted twice with 2N sodium hydroxide to remove a small amount of unreacted methyl-5-acetylsalicylate. The solution was then washed with dilute phosphoric acid, water, dilute sodium bicarbonate, and brine, dried over sodium sulfate, filtered, and evaporated. The crude product was purified by flash chromatography (350g silica, 3:1 hexane/ethyl acetate) to give the title compound.

1-[4-(2-furyl)3-(methoxycarbonyl)phenyl]-4,4,4-trifluoro-1,3-butanedione

- 20 [0164] 4-(2-furyl)-3-(methoxycarbonyl)phenyl-1-ethanone (1.36g, 5.57mmol) was dissolved in MTBE (30ml) at room temperature under nitrogen. Ethyl trifluoroacetate (0.87g, 6.1 mmol) was added followed by a suspension of sodium methoxide (0.36g, 6.7mmol) in methanol (5ml). After 2 hours of stirring, ethyl trifluoroacetate (2.03g, 14.3mmol) was added, followed by sodium methoxide (0.87g, 6.1mmol). After an additional 18 hours, the mixture was poured into stirring ethyl acetate and dilute hydrochloric acid. The organic layer was washed with water and brine, dried over sodium sulfate, filtered, and evaporated to give the title compound.

4-(2-furyl)-3-(carboxy)phenyl-1-ethanone

- 35 [0165] 4-(2-furyl)-3-(methoxycarbonyl)phenyl-1-ethanone (3.85g, 15.78mmol) was heated to reflux in 20% methanolic potassium hydroxide (200ml) for 15 minutes. Most of the methanol was removed under reduced pressure. The residue was dissolved in water and washed with methylene chloride. The aqueous solution was acidified to pH 1 with 12N hydrochloric acid and the product extracted with ethyl acetate. The organic solution was washed with water and brine, dried over sodium sulfate, filtered, and evaporated. The crude product was recrystallized from toluene to give the title compound.

4-(2-furyl)-3-(carboxamido)phenyl-1-ethanone

- 40 [0166] 4-(2-furyl)-3-(carboxy)phenyl-1-ethanone (1.79g, 7.79mmol) was stirred in methylene chloride (60ml) at room temperature under nitrogen. Oxalyl chloride (1.19g, 9.35mmol) was added, followed by 1 drop of N,N-dimethylformamide. The mixture was stirred 1 hour, then concentrated ammonium hydroxide (25ml) was added with vigorous stirring. After 15 minutes the mixture was suction filtered. The methylene chloride was separated from the aqueous layer and evaporated. The residue was added to the precipitate from the filtration and taken up in hot acetic acid. After cooling, the mixture was filtered to remove some precipitated inorganic salts, and the filtrate was evaporated. The residue was triturated with methanol and dried under vacuum to give the title compound.

1-[4-(2-furyl)3-(carboxamido)phenyl]-4,4,4-trifluoro-1,3-butanedione

- 50 [0167] 4-(2-furyl)-3-(carboxamido)phenyl-1-ethanone (146mg, 0.64mmol) was dissolved in dimethoxyethane (10ml). Ethyltrifluoroacetate (271 mg, 1.91mmol) was added, followed by sodium methoxide (234mg, 4.34mmol). The mixture was stirred 18 hours at room temperature under nitrogen, then poured into stirring ethyl acetate/dilute hydrochloric acid. The organic layer was separated, washed with water and brine, dried over sodium sulfate, filtered, and evaporated to give the title compound.

2-Hydroxy-4-acetylbenzonitrile

[0168] 5-acetylsalicylamide (10.04g, 56mmol) and diphosgene (18.4g, 93mmol) were heated in dioxane (65ml) to 70°C under nitrogen for 18 hours. The mixture was cooled, cautiously poured into cold water (700ml) and stirred for 1 hour to destroy excess diphosgene reagent. The mixture was extracted with ethyl acetate, and the organic solution washed with water and brine, dried over sodium sulfate, filtered, and evaporated. The residue was recrystallized from toluene/acetonitrile to give the title compound.

2-Cyano-4-acetylphenyltrifluoromethanesulfonate

[0169] 2-Hydroxy-4-acetylbenzonitrile (3.0g, 18.63mmol) was stirred in dry methylene chloride (80ml) in a 3-neck flask fitted with an internal thermometer, addition funnel, and nitrogen inlet. Triethylamine (2.26g, 22.4mmol) was added. After dissolution was complete, the solution was cooled to -40°C under nitrogen. A solution of trifluoromethanesulfonic anhydride (5.52g, 19.6mmol) in methylene chloride (10ml) was added dropwise over 15 minutes, maintaining the internal temperature below -35°C. The mixture was stirred 15 minutes, and water (90ml) was added. The methylene chloride layer was separated, washed with brine, dried over sodium sulfate, filtered, and evaporated to give the title compound, which was used without further purification.

4-(2-furyl)-3-(cyano)phenyl-1-ethanone

[0170] The title compound was prepared according to the procedure for preparation of 4-(2-furyl)-3-(methoxycarbonyl)phenyl-1-ethanone using 2-Cyano-4-acetylphenyl trifluoromethanesulfonate instead of 2-Methoxycarbonyl-4-acetylphenyl trifluoromethanesulfonate.

1-[4-(2-furyl)3-(cyano)phenyl]-4,4,4-trifluoro-1,3-butanedione

[0171] The title compound was prepared according to the procedure for preparation of 1-[4-(2-furyl)3-(carboxamido)phenyl]-4,4,4-trifluoro-1,3-butanedione, using 4-(2-furyl)3-(cyano)phenyl-1-ethanone instead of 4-(2-furyl)-3-(carboxamido)phenyl-1-ethanone.

30

35

40

45

50

55

Table 1a

Example	Structure	MP/°C	NMR Data	IR	MS
5		81.0-83.0	¹ H-NMR (CDCl ₃) δ: 8.93 (d, J = 2 Hz, 1H), 8.72 (dd, J = 1, 3 Hz, 1H), 8.09 (dd, J = 1, 8 Hz, 1H), 7.92 (dd, J = 3, 9 Hz, 1H), 7.73 (d, J = 8 Hz, 1H), 7.46 (d, J = 2 Hz, 1H), 7.29-7.28 (m, 1H), 7.15 (d, J = 8 Hz, 1H), 3.23 (s, 3H), 2.49 (s, 3H)		Anal.Calcd.for.C ₂₀ H ₁₄ ClF ₃ N ₄ O ₂ S ₂ :HCl, 0.45Hexane: C, 46.63; H, 3.50; N, 9.08. Found: C, 46.94; H, 3.38; N, 10.23. MS (EI) : m/z 498(M ⁺)
6		225.0-227.0	¹ H-NMR (CDCl ₃) δ: 8.92 (d, J = 2 Hz, 1H), 8.73 (d, J = 2 Hz, 1H), 8.34 (dd, J = 3, 9 Hz, 1H), 8.04-7.97 (m, 3H), 7.66 (d, J = 2 Hz, 1H), 7.41 (d, J = 8 Hz, 2H), 3.10 (s, 3H)		Anal.Calcd.for.C ₁₉ H ₁₂ ClF ₃ N ₄ O ₂ S ₂ : 0.5Hexane: C, 47.27; H, 2.58; N, 11.49. Found: C, 46.89; H, 2.93; N, 11.34. MS (EI) : m/z 484(M ⁺)
7		170.5-171	¹ H-NMR (CDCl ₃) δ: 8.92 (d, J = 2 Hz, 1H), 8.74 (d, J = 2 Hz, 1H), 8.11 (d, J = 8 Hz, 1H), 8.06 (d, J = 8 Hz, 2H), 7.95 (dd, J = 8, 2Hz, 1H), 7.60 (d, J = 2 Hz, 1H), 7.38 (d, J = 8 Hz, 2H), 3.24 (s, 3H)		MS (EI) : m/z 468(M ⁺)
8			¹ H-NMR (CDCl ₃) δ: 8.88 (s, 1H), 8.81 (d, J = 3Hz, 1H), 8.37 (dd, J = 2, 9Hz, 1H), 8.07 (d, J = 9 Hz, 1H), 7.92 (s, 1H), 7.38 (d, J = 8 Hz, 1H), 7.31 (s, 1H), 7.12 (d, J = 8 Hz, 1H), 6.79 (s, 1H), 3.12 (s, 3H), 2.42 (s, 3H), 8.93 (d, J = 2 Hz, 1H), 8.72 (dd, J = 1, 3 Hz, 1H), 8.09 (dd, J = 1, 8 Hz, 1H), 7.92 (dd, J = 3, 9 Hz, 1H), 7.73 (d, J = 8 Hz, 1H), 7.46 (d, J = 2 Hz, 1H), 7.29-7.28 (m, 1H), 7.15 (d, J = 8 Hz, 1H), 3.23 (s, 3H), 2.49 (s,		Anal.Calcd.for.C ₂₀ H ₁₅ F ₃ N ₄ O ₂ S ₂ : 0.3H ₂ O: C, 51.12; H, 3.35; N, 11.92. Found: C, 50.84; H, 3.72; N, 12.10. MS (EI) : m/z 464(M ⁺)

Example	Structure	MPC	NMR Data	IR	MS
9		154.0-155.0	$^1\text{H-NMR}$ (CDCl_3) δ : 8.80 (d, $J = 2$ Hz, 1H), 8.35 (dd, $J = 3, 9$ Hz, 1H), 8.02-7.98 (m, 2H), 7.89 (d, $J = 1$ Hz, 1H), 7.87 (d, $J = 8$ Hz, 1H), 7.29-7.28 (brm, 1H), 7.15 (dd, $J = 2, 9$ Hz, 1H), 6.80 (s, 1H), 3.11 (s, 3H), 2.48 (s, 3H).		Anal. Calcd. for $\text{C}_{20}\text{H}_{15}\text{F}_3\text{NaO}_3\text{S}, 0.4\text{H}_2\text{O}$: C, 53.10; H, 3.67; N, 12.14. Found: C, 53.23; H, 3.53; N, 11.84. MS (EI): m/z 448(M^+)
10		214-215	$^1\text{H-NMR}$ (CDCl_3) δ : 8.92 (d, $J = 2.0$ Hz, 1H), 8.71 (d, $J = 1.6$ Hz, 1H), 8.30 (dd, $J = 8.6$ Hz, 1H), 8.05 (d, $J = 8.6$ Hz, 1H), 7.54 (s, 1H), 7.43 (d, $J = 2.0$ Hz, 1H), 7.13 (s, 1H), 6.69 (s, 1H), 3.09 (s, 3H), 2.43 (s, 3H), 2.04 (s, 3H).		Anal. Calcd. for $\text{C}_{21}\text{H}_{17}\text{F}_3\text{NaO}_2\text{S}_2\text{O} \cdot 0.5\text{H}_2\text{O}$: C, 51.74; H, 3.72; N, 11.49. Found: C, 51.42; H, 3.87; N, 11.28.
11		223-224	$^1\text{H-NMR}$ (CDCl_3) δ : 8.92 (d, $J = 2.0$ Hz, 1H), 8.81 (d, $J = 2.5$ Hz, 1H), 8.37 (dd, $J = 2.5, 8.6$ Hz, 1H), 8.09, (s, 1H), 7.96 (d, $J = 8.6$ Hz, 1H), 7.69 (d, $J = 7.7$ Hz, 1H), 7.46 (d, $J = 2.0$ Hz, 1H), 7.38 (d, $J = 1.0$ Hz, 1H), 7.20 (dd, $J = 1.8, 8.2$ Hz, 3.12 (s, 3H), 2.50 (s, 3H)		Anal. Calcd. for $\text{C}_{20}\text{H}_{15}\text{NaO}_2\text{S}_2 \cdot 0.1\text{H}_2\text{O}$: C, 56.75; H, 3.62; N, 16.54. Found: C, 56.62; H, 3.87; N, 16.22.
12		144-145	$^1\text{H-NMR}$ (CDCl_3) δ : 8.91 (d, $J = 2.0$ Hz, 1H), 8.82 (d, $J = 2.3$ Hz, 2H), 8.34 (dd, $J = 2.5, 8.6$ Hz, 1H), 8.04 (d, $J = 8.4$ Hz, 1H), 7.62 (d, $J = 8.1$ Hz, 1H), 7.42 (d, $J = 2.0$ Hz, 1H), 7.29 (d, $J = 1.3$ Hz, 1H), 7.12 (dd, $J = 1.5, 7.7$ Hz, 1H), 7.07 (s, 1H), 4.00 (s, 3H), 3.11 (s, 3H), 2.47 (s, 3Hz).		Anal. Calcd. for $\text{C}_{21}\text{H}_{17}\text{NaO}_2\text{S}_2 \cdot 0.1\text{H}_2\text{O}$: C, 55.27; H, 4.02; N, 12.28. Found: C, 55.02; H, 4.12; N, 12.14.

Example	Structure	MP/°C	NMR Data	IR	MS
13		163-164	$^1\text{H-NMR}$ (CDCl_3) δ : 8.93 (d, J = 2.0 Hz, 1H), 8.27 (dd, J = 2.3 Hz, 1H), 8.19 (d, J = 8.7 Hz, 1H), 7.94 (d, J = 8.7 Hz, 1H), 7.87 (d, J = 7.9 Hz, 1H), 7.45 (d, J = 2.0 Hz, 1H), 2.0 (s, 1H), 7.13 (d, J = 8.4 Hz, 1H), 3.08 (s, 3H), 1.13 (t, J = 7.6 Hz, 3H).		Anal. Calcd. for $\text{C}_{22}\text{H}_{19}\text{F}_3\text{N}_3\text{O}_2\text{S}_2$: C, 53.65; H, 3.89; N, 11.37. Found: C, 53.46; H, 4.05; N, 11.33.
14					
15		160.0-161.1	$^1\text{H-NMR}$ (CDCl_3) δ : 8.79 (d, J = 2 Hz, 1H), 8.36 (dd, J = 2, 9 Hz, 1H), 8.04 (dd, J = 1, 9 Hz, 1H), 7.96 (d, J = 3 Hz, 1H), 7.76 (d, J = 8 Hz, 1H), 7.48 (d, J = 3 Hz, 1H), 7.34-7.32 (brm, 1H), 7.15 (dd, J = 2, 8 Hz, 1H), 6.82 (s, 1H), 3.11 (s, 3H), 2.62 (s, 3H).		$^{\text{MS}}(\text{EI}): m/z$ 464 (M ⁺)
16		165.0-166.0	$^1\text{H-NMR}$ (CDCl_3) δ : 8.84 (d, J = 3 Hz, 1H), 8.35 (dd, J = 3, 9 Hz, 1H), 8.01 (d, J = 9 Hz, 1H), 7.40 (dd, J = 3, 5 Hz, 1H), 7.33-7.27 (m, 3H), 7.19 (dd, J = 1, 5 Hz, 1H), 7.08 (d, J = 8 Hz, 1H), 6.79 (s, 1H), 3.12 (s, 3H), 2.36 (s, 3H).		Anal. Calcd. for $\text{C}_{21}\text{H}_{16}\text{F}_3\text{N}_3\text{O}_2\text{S}_2$: C, 54.42; H, 3.48; N, 9.07. Found: C, 54.26; H, 3.64; N, 8.97.

EP 1 104 759 A1

Example	Structure	MP/°C	¹ H-NMR Data	IR	MS
33		174.0-176.0	¹ H-NMR (CDCl ₃) δ: 8.76 (d, J = 3 Hz, 1H), 8.12 (d, J = 8 Hz, 1H), 7.97 (dd, J = 2, 6 Hz, 1H), 7.92 (d, J = 8 Hz, 2H), 7.82 (d, J = 7 Hz, 1H), 7.54 (d, J = 8 Hz, 1H), 7.36-7.27 (m, 4H), 7.12 (s, 1H), 6.88 (s, 1H), 3.24 (s, 3H).		Anal.Calcd.for.C24H16ClF3N3O2S: C, 59.62; H, 3.34; N, 8.69. Found: C, 59.29; H, 3.50; N, 8.30.
34		155.0-156.0	¹ H-NMR (CDCl ₃) δ: 8.74 (d, J = 3 Hz, 1H), 8.12 (d, J = 8 Hz, 1H), 7.97 (dd, J = 3, 8 Hz, 1H), 7.56 (d, J = 9 Hz, 2H), 7.26 (d, J = 9 Hz, 2H), 7.15 (d, J = 4 Hz, 1H), 6.93 (d, J = 4 Hz, 1H), 6.84 (s, 1H), 3.24 (s, 3H).		Anal.Calcd.for.C20H13ClF3N3O2S2,0 2H2O: C, 49.27; H, 2.77; N, 8.62. Found: C, 48.96; H, 2.86; N, 8.59. MS (EI) : m/z 483 (M ⁺)
35		123.0-124.0	¹ H-NMR (CDCl ₃) δ: 8.75 (d, J = 2 Hz, 1H), 8.11 (dd, J = 4, 9 Hz, 1H), 7.96 (dd, J = 3, 9 Hz, 1H), 7.59 (d, J = 8 Hz, 2H), 7.24-7.15 (m, 3H), 6.83 (s, 1H), 6.76 (dd, J = 1, 4 Hz, 1H), 3.24 (s, 3H), 2.53 (s, 3H).		Anal.Calcd.for.C21H16F3N3O2S2,0.1 H2O: C, 54.21; H, 3.51; N, 9.03. Found: C, 53.97; H, 3.55; N, 9.06. MS (EI) : m/z 463 (M ⁺)
36		209-212	¹ H-NMR (CDCl ₃) δ: 8.38 (d, J = 9.2 Hz, 1H), 8.32 (d, J = 9.2 Hz, 1H), 7.70 (d, J = 8.6 Hz, 2H), 7.51 (d, J = 1.8 Hz, 1H), 7.35 (d, J = 8.6 Hz, 2H), 6.85 (s, 1H), 6.74 (d, J = 3.3 Hz, 1H), 6.50 (dd, J = 1.8, 3.3 Hz, 1H), 3.39 (s, 3H).		Anal. Calcd. for C ₁₀ H ₁₃ N ₄ O ₃ F ₅ S: C, 52.53; H, 3.02; N, 12.90. Found: C, 52.42; H, 3.13; N, 12.82.

EP 1 104 759 A1

5

10

15

20

25

30

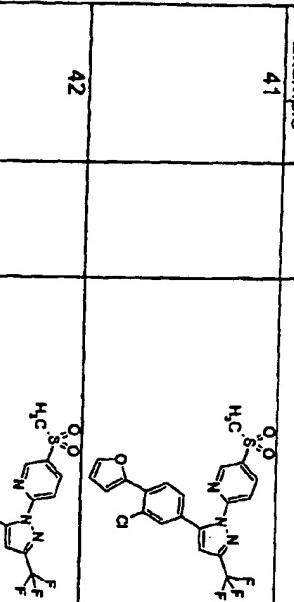
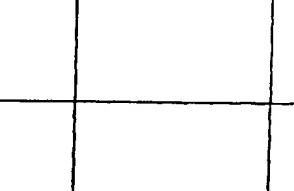
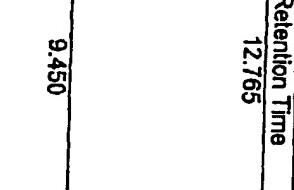
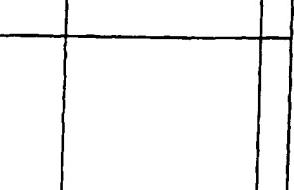
35

40

45

50

55

Example		Retention Time	Mass ($M+1$)
41		12.765	468.3, 470.3
42		9.450	465.3
43		11.059	434.3
44		8.742	465.3

EP 1 104 759 A1

Example		<chem>H3C-S(=O)(=O)O</chem>	Retention Time	Mass (M+1)
50			10.530	459.3
51				
52			8.992	416.3
53			9.277	416.3
54			11.007	450.3, 452.3
			9.657	459.3

Example		Retention Time	Mass (M+1)
55		11.826	452.3
56		10.053	434.3
57		9.628	502.3, 504.3
58		9.372	451.3

5

10

15

20

25

30

35

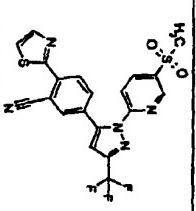
40

45

50

55

Example	Retention Time	Mass (M+1)
59	8.814	476.3



Claims

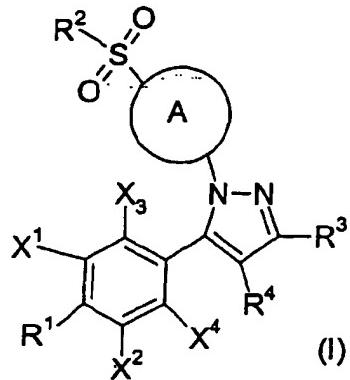
1. A compound of the following formula:

5

10

15

20



or a pharmaceutically acceptable salt thereof, wherein

A is selected from the group consisting of

- a) (5- to 6-membered)-heteroaryl containing 1 to 4 ring heteroatoms independently selected from -N=, -NR', -O-, or -S-, wherein said heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl may optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-;
- b) (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR', -S- or -O-; wherein said heteroaryl is fused to a saturated, partially saturated or aromatic (5- to 7-membered)-carbocyclic ring; wherein either of said (5- to 6-membered)-heteroaryl ring or said fused saturated, partially saturated or aromatic (5- to 7-membered)-carbocyclic ring may optionally be substituted with 1 to 2 substituents per ring, wherein said substituents are independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; and
- c) (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR', -S- or -O-; wherein said heteroaryl is fused to a (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR', -S- or -O-; wherein either of said (5- to 6-membered)-heteroaryl or said fused (5- to 6-membered)-heteroaryl is optionally substituted with one to two substituents per ring, wherein said substituents are independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl may optionally be substituted with 1 to 3 substituents independently selected

from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-;

5

R¹ is selected from the group consisting of

- a) (5- to 6-membered)-heteroaryl containing 1 to 4 ring heteroatoms independently selected from -N=, -NR-, -O-, or -S-, wherein said heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-;
- b) (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR', -S- or -O-; wherein said heteroaryl is fused to a saturated, partially saturated or aromatic (5- to 7-membered)-carbocyclic ring; wherein either of said (5- to 6-membered)-heteroaryl ring or said fused saturated, partially saturated or aromatic (5- to 7-membered)-carbocyclic ring is optionally substituted with 1 to 2 substituents per ring, wherein said substituents are independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; and
- c) (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR', -S-, or -O-; wherein said heteroaryl is fused to a (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR', -S- or -O-; wherein either of said (5- to 6-membered)-heteroaryl or said fused (5- to 6-membered)-heteroaryl is optionally substituted with one to two substituents per ring, wherein said substituents are independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-;

R² is selected from the group consisting of (C₁-C₄)alkyl optionally substituted with 1 to 3 halo;

R³ and R⁴ are independently selected from the group consisting of hydrogen, halo, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-(C=O)-, cyano, nitro, carboxy, (C₁-C₄)alkoxy-(C=O)-, amino-(C=O)-, (C₁-C₄)alkyl-amino-(C=O)-, di[(C₁-C₄)alkyl]-amino-(C=O)-, N-[(C₁-C₄)alkyl]-N-phenyl-amino-(C=O)-, N-[(C₁-C₄)alkyl]-N-[(5- to 6-membered)-heteroaryl]-amino-(C=O)-, wherein said (5- to 6-)membered heteroaryl contains 1 to 4 heteroatoms independently selected from -N=, -NR', -O- and -S-; wherein each of said (C₁-C₄)alkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, phenyl, (C₁-C₄)alkoxy and (5- to 6-membered)-heteroaryl containing 1 to 4 heteroatoms independently selected from -N=, -NR', -O- and -S-; wherein each of said R' is independently hydrogen or (C₁-C₄)alkyl; and

X¹, X², X³ and X⁴ are independently selected from the group consisting of hydrogen, halo, hydroxy, cyano,

5 m capto, carboxy, nitro, (C_1 - C_4)alkyl, (C_1 - C_4)alkoxy, (C_1 - C_4)alkyl-S-, (C_1 - C_4)alkyl-amino-, di[(C_1 - C_4)alkyl]-amino-, (C_1 - C_4)alkyl-(C=O)-, (C_1 - C_4)alkoxy-(C=O)- and amino-C(=O)-; wherein each said (C_1 - C_4)alkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, amino, (C_1 - C_4)alkyl-amino-, di[(C_1 - C_4)alkyl]-amino-, hydroxy, carboxy, amino-(C=O)-, (C_1 - C_4)alkyl-amino-C(=O)-, di[(C_1 - C_4)alkyl]-amino-C(=O)-, mercapto, (C_1 - C_4)alkyl-S- and (C_1 - C_4)alkoxy-(C=O)-.

2. A compound of Claim 1 wherein

10 A is (5- to 6-membered)- heteroaryl containing 1 to 4 ring heteroatoms independently selected from -N=, -NR'-, -O-, or -S-, wherein said heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C_1 - C_4)alkyl, (C_2 - C_4)alkynyl, (C_1 - C_4)alkoxy, (C_1 - C_4)alkyl-S-, amino, (C_1 - C_4)alkylamino, di[(C_1 - C_4)alkyl]amino, amido, (C_1 - C_4)alkylamido, di[(C_1 - C_4)alkyl]amido, (C_1 - C_4)alkyl-(C=O)-O-, (C_1 - C_4)alkyl-(C=O)-N(R'), formyl, (C_1 - C_4)alkyl-(C=O)- and (C_1 - C_4)alkoxy-(C=O)-; wherein R' is hydrogen or (C_1 - C_4)alkyl; wherein each of said (C_1 - C_4)alkyl may 15 optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C_1 - C_4)alkyl, (C_2 - C_4)alkenyl, (C_1 - C_4)alkynyl, (C_1 - C_4)alkyl-S-, amino, (C_1 - C_4)alkylamino, di[(C_1 - C_4)alkyl]amino, amido, (C_1 - C_4)alkylamido, di[(C_1 - C_4)alkyl]amido, (C_1 - C_4)alkyl-(C=O)-O-, (C_1 - C_4)alkyl-(C=O)-N(R')-, formyl, (C_1 - C_4)alkyl-(C=O)- and (C_1 - C_4)alkoxy-(C=O)-; wherein preferred A is selected from the group consisting of (5- to 6-membered)- heteroaryl containing 1 to 4 20 ring heteroatoms independently selected from -N=, -NR'-, -O-, or -S-, wherein said heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of halo, (C_1 - C_4)alkyl, (C_1 - C_4)alkoxy, (C_1 - C_4)alkyl-S-, (C_1 - C_4)alkylamino, di[(C_1 - C_4)alkyl]amino; wherein R' is hydrogen or (C_1 - C_4)alkyl; wherein each of said (C_1 - C_4)alkyl may 25 optionally be substituted with 1 to 3 halo; and R¹ is (5- to 6-membered)-heteroaryl containing 1 to 4 ring heteroatoms independently selected from -N=, -NR'-, -O-, or -S-, wherein said heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C_1 - C_4)alkyl, (C_2 - C_4)alkenyl, (C_2 - C_4)alkynyl, (C_1 - C_4)alkoxy, (C_1 - C_4)alkyl-S-, amino, (C_1 - C_4)alkylamino, di[(C_1 - C_4)alkyl]amino, amido, (C_1 - C_4)alkylamido, di[(C_1 - C_4)alkyl]amido, (C_1 - C_4)alkyl-(C=O)-O-, (C_1 - C_4)alkyl-(C=O)-N(R')-, formyl, (C_1 - C_4)alkyl-(C=O)- and (C_1 - C_4)alkoxy-(C=O)-; wherein R' is hydrogen or (C_1 - C_4)alkyl; wherein each of said (C_1 - C_4)alkyl is 30 optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C_1 - C_4)alkyl, (C_2 - C_4)alkenyl, (C_1 - C_4)alkynyl, (C_1 - C_4)alkyl-S-, amino, (C_1 - C_4)alkylamino, di[(C_1 - C_4)alkyl]amino, amido, (C_1 - C_4)alkylamido, di[(C_1 - C_4)alkyl]amido, (C_1 - C_4)alkyl-(C=O)-O-, (C_1 - C_4)alkyl-(C=O)-N(R')-, formyl, (C_1 - C_4)alkyl-(C=O)- and (C_1 - C_4)alkoxy-(C=O)-; wherein preferred R¹ is selected from the group consisting of (5- to 6-membered)- heteroaryl containing 1 to 4 ring 35 heteroatoms independently selected from -N=, -NR'-, -O-, or -S-, wherein said heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of halo, (C_1 - C_4)alkyl, (C_1 - C_4)alkoxy, (C_1 - C_4)alkyl-(C=O)-, hydroxy, cyano and amino; wherein R' is hydrogen or (C_1 - C_4)alkyl; wherein each of said (C_1 - C_4)alkyl may optionally be substituted with 1 to 3 halo.

40 3. A compound of Claim 1 wherein

A is (5- to 6-membered)- heteroaryl containing 1 to 4 ring heteroatoms independently selected from -N=, -NR'-, -O-, or -S-, wherein said heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C_1 - C_4)alkyl, (C_2 - C_4)alkenyl, (C_2 - C_4)alkynyl, (C_1 - C_4)alkoxy, (C_1 - C_4)alkyl-S-, amino, (C_1 - C_4)alkylamino, di[(C_1 - C_4)alkyl]amino, amido, (C_1 - C_4)alkylamido, di[(C_1 - C_4)alkyl]amido, (C_1 - C_4)alkyl-(C=O)-O-, (C_1 - C_4)alkyl-(C=O)-N(R')-, formyl, (C_1 - C_4)alkyl-(C=O)- and (C_1 - C_4)alkoxy-(C=O)-; wherein R' is hydrogen or (C_1 - C_4)alkyl; wherein each of said (C_1 - C_4)alkyl may 45 optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C_1 - C_4)alkyl, (C_2 - C_4)alkenyl, (C_1 - C_4)alkynyl, (C_1 - C_4)alkyl-S-, amino, (C_1 - C_4)alkylamino, di[(C_1 - C_4)alkyl]amino, amido, (C_1 - C_4)alkylamido, di[(C_1 - C_4)alkyl]amido, (C_1 - C_4)alkyl-(C=O)-O-, (C_1 - C_4)alkyl-(C=O)-N(R')-, formyl, (C_1 - C_4)alkyl-(C=O)- and (C_1 - C_4)alkoxy-(C=O)-; wherein preferred A is selected from the group consisting of (5- to 6-membered)- heteroaryl containing 1 to 4 50 ring heteroatoms independently selected from -N=, -NR'-, -O-, or -S-, wherein said heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of halo, (C_1 - C_4)alkyl, (C_1 - C_4)alkoxy, (C_1 - C_4)alkyl-(C=O)-, hydroxy, cyano and amino; wherein R' is hydrogen or (C_1 - C_4)alkyl; wherein each of said (C_1 - C_4)alkyl may 55 optionally be substituted with 1 to 3 halo; and R¹ is (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR'-, -S- or -O-; wherein said heteroaryl is fused to a saturated, partially saturated or

5 aromatic (5- to 7-membered)-carbocyclic ring; wherein either of said (5- to 6-membered)-heteroaryl ring or said fused saturated, partially saturated or aromatic (5- to 7-membered)-carbocyclic ring is optionally substituted with 1 to 2 substituents per ring, wherein said substituents are independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein preferred R' is selected from the group consisting of (5- to 6-membered)-heteroaryl containing 1 ring heteroatom selected from the group consisting of -N=, -NR', -S- or -O-; wherein said heteroaryl is fused to an aromatic (6-membered)-carbocyclic ring; wherein either of said (5- to 6-membered)-heteroaryl ring or said fused aromatic (6-membered)-carbocyclic ring may optionally be substituted with 1 to 2 substituents per ring, wherein said substituents are independently selected from the group consisting of halo and (C₁-C₄)alkyl; wherein R' is hydrogen or (C₁-C₄)alkyl.

4. A compound of Claim 1 wherein

20 A is (5- to 6-membered)-heteroaryl containing 1 to 4 ring heteroatoms independently selected from -N=, -NR', -O-, or -S-, wherein said heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl may optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein preferred A is selected from the group consisting of (5- to 6-membered)-heteroaryl containing 1 to 4 ring heteroatoms independently selected from -N=, -NR', -O-, or -S-, wherein said heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of halo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl may optionally be substituted with 1 to 3 halo; and

25 R' is (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR', -S-, or -O-; wherein said heteroaryl is fused to a (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR', -S- or -O-; wherein either of said (5- to 6-membered)-heteroaryl or said fused (5- to 6-membered)-heteroaryl is optionally substituted with one to two substituents per ring, wherein said substituents are independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-.

30 40 45 50

5. A compound of Claim 1 wherein

55 A is (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR', -S- or -O-; wherein said heteroaryl is fused to a saturated, partially saturated or aromatic (5- to 7-membered)-carbocyclic ring; wherein either of said (5- to 6-membered)-heteroaryl ring or said fused saturated, partially saturated or aromatic (5- to 7-membered)-carbocyclic ring may optionally be substituted with 1 to 2 substituents per ring, wherein said substituents are independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-.

do, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R'), formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; and R¹ is (5- to 6-membered)-heteroaryl containing 1 to 4 ring heteroatoms independently selected from -N=, -NR'-, -O-, or -S-, wherein said heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein preferred R¹ is selected from the group consisting of (5- to 6-membered)-heteroaryl containing 1 to 4 ring heteroatoms independently selected from -N=, -NR'-, -O-, or -S-, wherein said heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of halo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-(C=O)-, hydroxy, cyano and amino; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl may optionally be substituted with 1 to 3 halo.

6. A compound of Claim 1 wherein

A is (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR'-, -S- or -O-; wherein said heteroaryl is fused to a saturated, partially saturated or aromatic (5- to 7-membered)-carbocyclic ring; wherein either of said (5- to 6-membered)-heteroaryl ring or said fused saturated, partially saturated or aromatic (5- to 7-membered)carbocyclic ring may optionally be substituted with 1 to 2 substituents per ring, wherein said substituents are independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; and R¹ is (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR'-, -S- or -O-; wherein said heteroaryl is fused to a saturated, partially saturated or aromatic (5- to 7-membered)-carbocyclic ring; wherein either of said (5- to 6-membered)-heteroaryl ring or said fused saturated, partially saturated or aromatic (5- to 7-membered)-carbocyclic ring is optionally substituted with 1 to 2 substituents per ring, wherein said substituents are independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein preferred R¹ is selected from the group consisting of (5- to 6-membered)-heteroaryl containing 1 ring heteroatom selected from the group consisting of -N=, -NR'-, -S- or -O-; wherein said heteroaryl is fused to an aromatic (6-membered)-carbocyclic ring; wherein either of said (5- to 6-membered)-heteroaryl ring or said fused aromatic (6-membered)-carbocyclic ring may optionally be substituted with 1 to 2 substituents per ring, wherein said substituents are independently selected from the group consisting of halo and (C₁-C₄)alkyl; wherein R' is hydrogen or (C₁-C₄)alkyl.

7. A compound of Claim 1 wherein

A is (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR', -S- or -O-; wherein said heteroaryl is fused to a saturated, partially saturated or aromatic (5- to 7-membered)-carbocyclic ring; wherein either of said (5- to 6-membered)-heteroaryl ring or said fused saturated, partially saturated or aromatic (5- to 7-membered)-carbocyclic ring may optionally be substituted with 1 to 2 substituents per ring, wherein said substituents are independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R'), formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O); wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₁-C₄)alkynyl, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R'), formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O); and R¹ is (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR', -S-, or -O-; wherein said heteroaryl is fused to a (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR', -S- or -O-; wherein either of said (5- to 6-membered)-heteroaryl or said fused (5- to 6-membered)-heteroaryl is optionally substituted with one to two substituents per ring, wherein said substituents are independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R'), formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O); wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₁-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R'), formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O).

8. A compound of Claim 1 wherein

A is (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR', -S-, or -O-; wherein said heteroaryl is fused to a (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR', -S- or -O-; wherein either of said (5- to 6-membered)-heteroaryl or said fused (5- to 6-membered)-heteroaryl is optionally substituted with one to two substituents per ring, wherein said substituents are independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R'), formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O); wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl may optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R'), formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O); and R¹ is (5- to 6-membered)-heteroaryl containing 1 to 4 ring heteroatoms independently selected from -N=, -NR', -O-, or -S-, wherein said heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R'), formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O); wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R'), formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O); wherein preferred R¹ is selected from the group consisting of (5- to 6-membered)-heteroaryl containing 1 to 4 ring heteroatoms independently selected from -N=, -NR', -O-, or -S-, wherein said heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of halo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-(C=O)-, hydroxy, cyano and amino; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl may optionally be substituted with 1 to 3 halo.

9. A compound of Claim 1 wher in

A is (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR'-, -S-, or -O-; wherein said heteroaryl is fused to a (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR'-, -S- or -O-; wherein either of said (5- to 6-membered)-heteroaryl or said fused (5- to 6-membered)-heteroaryl is optionally substituted with one to two substituents per ring, wherein said substituents are independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl may optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; and R¹ is (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR'-, -S- or -O-; wherein said heteroaryl is fused to a saturated, partially saturated or aromatic (5- to 7-membered)-carbocyclic ring; wherein either of said (5- to 6-membered)-heteroaryl ring or said fused saturated, partially saturated or aromatic (5- to 7-membered)-carbocyclic ring is optionally substituted with 1 to 2 substituents per ring, wherein said substituents are independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein preferred R¹ is selected from the group consisting of (5- to 6-membered)-heteroaryl containing 1 ring heteroatom selected from the group consisting of -N=, -NR'-, -S- or -O-; wherein said heteroaryl is fused to an aromatic (6-membered)-carbocyclic ring; wherein either of said (5- to 6-membered)-heteroaryl ring or said fused aromatic (6-membered)-carbocyclic ring may optionally be substituted with 1 to 2 substituents per ring, wherein said substituents are independently selected from the group consisting of halo and (C₁-C₄)alkyl; wherein R' is hydrogen or (C₁-C₄)alkyl.

10. A compound of Claim 1 wherein

A is (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR'-, -S-, or -O-; wherein said heteroaryl is fused to a (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR'-, -S- or -O-; wherein either of said (5- to 6-membered)-heteroaryl or said fused (5- to 6-membered)-heteroaryl is optionally substituted with one to two substituents per ring, wherein said substituents are independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl may optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; and R¹ is (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR'-, -S- or -O-; wherein said heteroaryl is fused to a (5- to 6-membered)-heteroaryl containing 1 to 2 ring heteroatoms independently selected from the group consisting of -N=, -NR'-, -S- or -O-; wherein either of said (5- to 6-membered)-heteroaryl or said fused (5- to 6-membered)-heteroaryl is optionally substituted with one to two substituents per ring, wherein said substituents are independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R')-, formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-;

EP 1 104 759 A1

lamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R'), formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, cyano, mercapto, carboxy, nitro, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, amino, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino, amido, (C₁-C₄)alkylamido, di[(C₁-C₄)alkyl]amido, (C₁-C₄)alkyl-(C=O)-O-, (C₁-C₄)alkyl-(C=O)-N(R'), formyl, (C₁-C₄)alkyl-(C=O)- and (C₁-C₄)alkoxy-(C=O)-.

11. A compound of Claim 1 wherein

10 A is (5- to 6-membered)-heteroaryl containing 1 to 4 ring heteroatoms independently selected from -N=, -NR'-, -O-, or -S-, wherein said heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of halo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-S-, (C₁-C₄)alkylamino, di[(C₁-C₄)alkyl]amino; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl is optionally substituted with 1 to 3 halo;

15 R¹ is selected from the group consisting of

20 a) (5- to 6-membered)- heteroaryl containing 1 to 4 ring heteroatoms independently selected from -N=, -NR'-, -O-, or -S-, wherein said heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of halo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-(C=O)-, hydroxy, cyano and amino; wherein R' is hydrogen or (C₁-C₄)alkyl; wherein each of said (C₁-C₄)alkyl is optionally substituted with 1 to 3 halo; and

25 b) (5- to 6-membered)-heteroaryl containing 1 ring heteroatom selected from the group consisting of -N=, -NR'-, -S- or -O-; wherein said heteroaryl is fused to an aromatic (6-membered)-carbocyclic ring; wherein either of said (5- to 6-membered)-heteroaryl ring or said fused aromatic (6-membered)-carbocyclic ring may optionally be substituted with 1 to 2 substituents per ring, wherein said substituents are independently selected from the group consisting of halo and (C₁-C₄)alkyl; wherein R' is hydrogen or (C₁-C₄)alkyl;

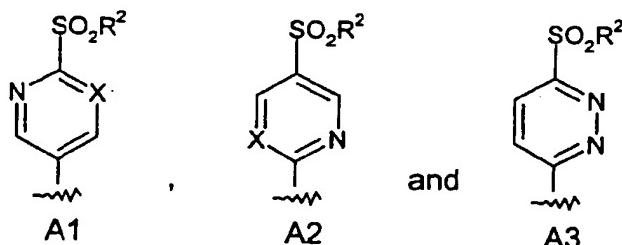
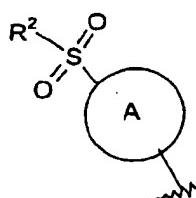
R² is (C₁-C₄)alkyl;

30 R³ and R⁴ are each independently selected from hydrogen; halo; (C₁-C₄)alkyl optionally substituted with 1 to 3 halo; (C₁-C₄)alkoxy; (C₁-C₄)alkyl-O-C(=O)- and cyano; and

X¹, X², X³, and X⁴, are each independently selected from hydrogen; halo; (C₁-C₄)alkyl optionally substituted with 1 to 3 halo; cyano and (C₁-C₄)alkoxy.

12. A compound according to Claim 11, wherein

35 Is selected from the group consisting of



55 wherein X is CH or N, and the heteroaryl moiety is unsubstituted, mono-, di- or tri-substituted with substituents

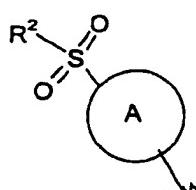
independently selected from the group consisting of halo and (C₁-C₄)alkyl;

5 R¹ is heteroaryl selected from the group consisting of furyl, thiazolyl, oxazolyl, thienyl, tetrazolyl, triazolyl, imidazolyl, benzofuranyl and benzothienyl, wherein said heteroaryl is unsubstituted, mono-, di- or tri-substituted with substituents independently selected from the group consisting of halo and (C₁-C₄)alkyl;
R² is methyl;

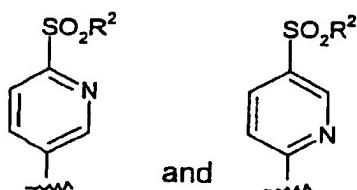
R³ and R⁴ are independently selected from the group consisting of hydrogen, halo and (C₁-C₄)alkyl optionally substituted with 1 to 3 halo; and

10 X¹, X², X³ and X⁴ are independently selected from the group consisting of hydrogen, halo, methyl, ethyl, methoxy, amino-C(=O)- and cyano.

13. A compound according to Claim 12 wherein



20 is selected from the group consisting of



wherein the heteroaryl moiety is optionally substituted with fluoro or methyl;

35 R¹ is selected from furyl, thiazolyl and oxazolyl;

R² is methyl;

R³ and R⁴ are each independently selected from hydrogen, chloro, fluoro, cyano, difluoromethyl and trifluoromethyl; and

40 X¹, X², X³ and X⁴ are independently selected from hydrogen, chloro, fluoro, methyl and cyano.

14. A compound according to Claim 13 selected from the group consisting of

45 4-chloro-5-[3-methyl-4-(4-thiazolyl)phenyl]-1-[5-(2-methylsulfonyl)pyridyl]-3-trifluoromethyl-1H-pyrazole;
5-(methylsulfonyl)-2-[5-[3-methyl-4-(1,3-thiazol-4-yl)phenyl]-3-trifluoromethyl-1H-pyrazol-1-yl]pyridine;
2-[5-[3-chloro-4-(1,3-thiazol-4-yl)phenyl]-3-trifluoromethyl-1H-pyrazol-1-yl]-5-(methylsulfonyl)pyridine;
5-[3-methyl-4-(1,3-thiazol-5-yl)phenyl]-1-[2-(5-methylsulfonyl)pyridyl]-3-trifluoromethyl-1H-pyrazole;
5-[3-methyl-4-(4-oxazolyl)phenyl]-1-[2-(5-methylsulfonyl)pyridyl]-3-trifluoromethyl-1H-pyrazole;
5-[3-methyl-4-(2-furyl)phenyl]-1-[2-(5-methylsulfonyl)pyridyl]-3-trifluoromethyl-1H-pyrazole;
5-[3-methyl-4-(2-oxazolyl)phenyl]-1-[2-(5-methylsulfonyl)pyridyl]-3-trifluoromethyl-1H-pyrazole;
50 2-[3-(difluoromethyl)-5-[3-methyl-4-(1,3-thiazol-4-yl)phenyl]-1H-pyrazol-1-yl]-5-(methylsulfonyl)pyridine;
2-[5-(3-chloro-4-furan-2-yl-phenyl)-3-trifluoromethyl-pyrazol-1-yl]-5-methanesulfonyl-pyridine;
2-[5-(4-furan-2-yl-phenyl)-3-trifluoromethyl-pyrazol-1-yl]-5-methanesulfonyl-pyridine;
5-[3-(chloro-4-furan-2-yl-phenyl)-3-trifluoromethyl-pyrazol-1-yl]-2-methanesulfonyl-pyridine;
5-[4-furan-2-yl-3-methyl-phenyl)-3-trifluoromethyl-pyrazol-1-yl]-2-methanesulfonyl-pyridine;
55 2-furan-2-yl-5-[2-(5-methanesulfonyl-pyridin-2-yl)-5-trifluoromethyl-2H-pyrazol-3-yl]-benzonitrile;
2-[5-(3-chloro-4-furan-2-yl-phenyl)-3-difluoromethyl-pyrazol-1-yl]-5-methanesulfonyl-pyridine;
2-[5-(3-fluoro-4-furan-2-yl-phenyl)-3-trifluoromethyl-pyrazol-1-yl]-5-methanesulfonyl-pyridine;
2-[3-difluoromethyl-5-(3-fluoro-4-furan-2-yl-phenyl)-pyrazol-1-yl]-5-methanesulfonyl-pyridine;

5-methanesulf nyl-2-[5-(4-thiazol-2-yl-phenyl)-3-trifluoromethyl-pyrazol-1-yl]-pyridine;
 5-[2-(5-methanesulfonyl-pyridin-2-yl)-5-trifluoromethyl-2H-pyrazol-3-yl]-2-thiazol-2-yl-benzonitrile;
 4-Fluoro-5-[4-(4-thiazolyl)phenyl]-1-[5-(2-methylsulfonyl)pyridyl]-3-trifluoromethyl-1H-pyrazole;
 2-[5-[2,5-dimethyl-4-(1,3-thiazol-4-yl)ph nyl]-3-(trifluoromethyl)-1H-pyrazol-1-yl]-5-(m thylsulfonyl)pyridin ;
 1-[5-(Methylsulfonyl)-2-pyridiny]-5-[3-methyl-4-(1,3-thiazol-4-yl)phenyl]-1H-pyrazole-4-carbonitrile;
 5-[3-Methyl-4-(1,3-thiazol-2-yl)phenyl]-1-[2-(5-methylsulfonyl)pyridyl]-3-trifluoromethyl-1 H-pyrazole;
 2-[5-[3-Fluoro-4-(1,3-thiazol-4-yl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-1-yl]-5-(methylsulfonyl)pyridine;
 2-Fluoro-3-(methylsulfonyl)-6-[5-[3-methyl-4-(1,3-thiazol-4-yl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridine; and
 10 2-Methyl-3-(methylsulfonyl)-6-[5-[3-methyl-4-(1,3-thiazol-4-yl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridine; or its salts.

15. A method of treating or preventing diseases or conditions according to Claim 15 wherein the disease or condition is selected from the group consisting of diseases or conditions in which prostaglandins are implicated as pathogens, pain, fever, inflammation, rheumatic fever, symptoms associated with influenza and other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis including rheumatoid arthritis, degenerative joint disease or osteoarthritis, gout and ankylosing spondylitis, bursitis, burns, injuries following surgical and dental procedures, disease or conditions associated with cellular neoplastic transformations and metastatic tumor growth, cancer, colorectal cancer, breast and skin cancer, familiar adenomatous polyposis, cyclooxygenase-mediated proliferation disorders, cyclooxygenase-mediated proliferation disorders in diabetic retinopathy and tumor angiogenesis, prostanoid-induced smooth muscle contraction mediated by synthesis of contractile prostanoids, dysmenorrhea, premature labor, asthma, eosinophil related disorders, neurodegenerative diseases, Alzheimer's and Parkinson's disease, bone loss, osteoarthritis, peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis, recurrent of gastrointestinal lesions, gastrointestinal bleeding, coagulation, anemia, hypoprothrombinemia, haemophilia, bleeding problems; kidney disease and conditions prior to surgery of taking of anticoagulants.

20. A pharmaceutical composition for treating a disease or condition selected from the group consisting of diseases or conditions in which prostaglandins are implicated as pathogens, pain, fever, inflammation, rheumatic fever, symptoms associated with influenza and other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis including rheumatoid arthritis, degenerative joint disease or osteoarthritis, gout and ankylosing spondylitis, bursitis, burns, injuries following surgical and dental procedures, disease or conditions associated with cellular neoplastic transformations and metastatic tumor growth, cancer, colorectal cancer, breast and skin cancer, familiar adenomatous polyposis, cyclooxygenase-mediated proliferation disorders, cyclooxygenase-mediated proliferation disorders in diabetic retinopathy and tumor angiogenesis, prostanoid-induced smooth muscle contraction mediated by synthesis of contractile prostanoids, dysmenorrhea, premature labor, asthma, eosinophil related disorders, neurodegenerative diseases, Alzheimer's and Parkinson's disease, bone loss, osteoarthritis, peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis, recurrent of gastrointestinal lesions, gastrointestinal bleeding, coagulation, anemia, hypoprothrombinemia, haemophilia, bleeding problems; kidney disease and conditions prior to surgery of taking of anticoagulants.

45

50

55



European Patent
Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number

which under Rule 45 of the European Patent Convention
shall be considered, for the purposes of subsequent
proceedings, as the European search report

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
D, A	US 5 756 529 A (TALLEY JOHN J ET AL) 26 May 1998 (1998-05-26) * abstract * * claim 1 *	1,15,16	C07D405/14 C07D417/14 C07D413/14 C07D409/14 C07D401/14 A61K31/506 A61P29/00
			TECHNICAL FIELDS SEARCHED (Int.Cl.)
			C07D A61K A61P
INCOMPLETE SEARCH			
The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.			
Claims searched completely :			
Claims searched incompletely :			
Claims not searched :			
Reason for the limitation of the search :			
Although claim 15 is directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	7 March 2001	Diederer, J	
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons S : member of the same patent family, corresponding document	

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 00 31 0356

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

07-03-2001

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5756529	A 26-05-1998	AU 718300 B	13-04-2000
		AU 7376896 A	17-04-1997
		BR 9610974 A	13-07-1999
		CA 2233620 A	03-04-1997
		CN 1202828 A	23-12-1998
		CZ 9800897 A	14-04-1999
		EP 0854723 A	29-07-1998
		JP 11514991 T	21-12-1999
		NO 981392 A	25-05-1998
		NZ 320919 A	28-10-1999
		PL 325952 A	17-08-1998
		WO 9711704 A	03-04-1997